





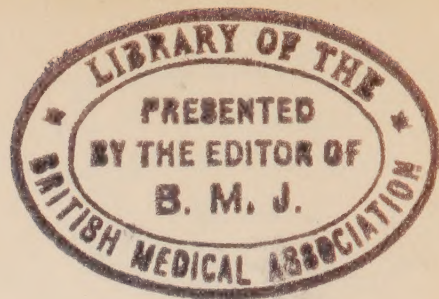
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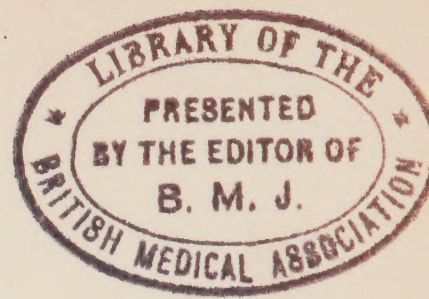
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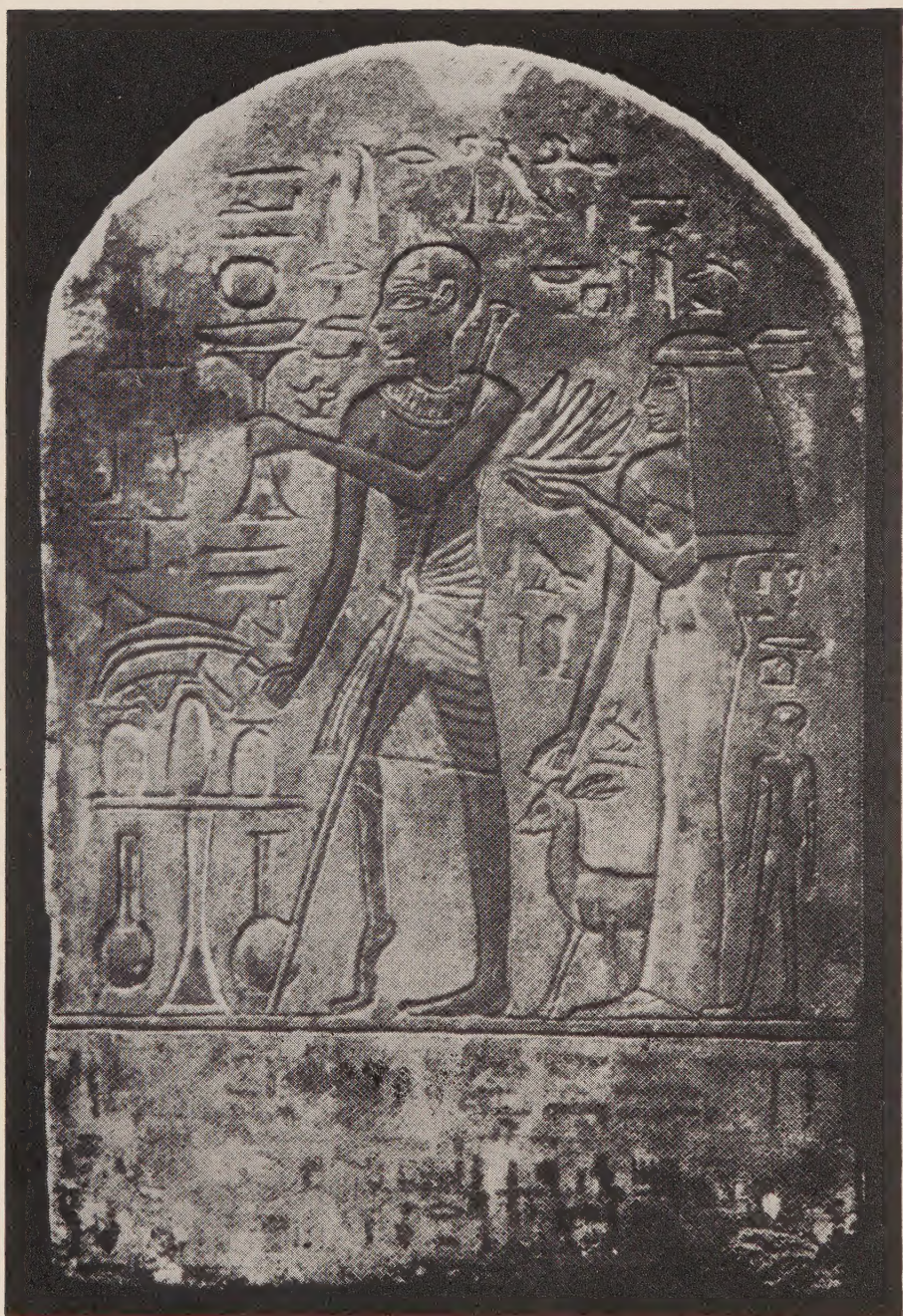












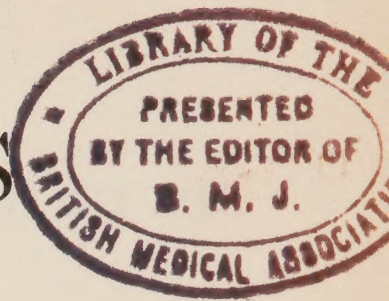
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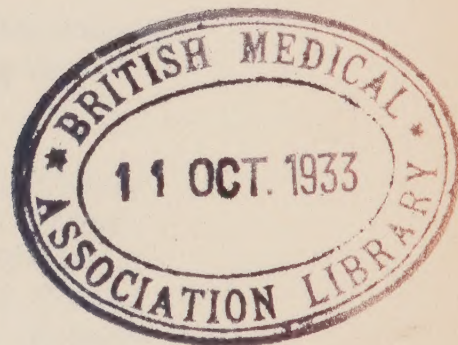


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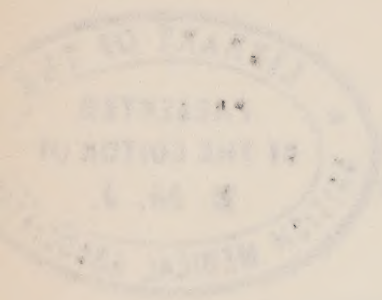


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OF INFANTILE PARALYSIS  
ORGANIZED BY JEREMIAH MILBANK



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## FOREWORD

If I venture at the suggestion of Dr. William H. Park to add a few words of mine to be included in this volume, it is chiefly to record the pleasure I have had in my association with him and his colleagues on the Committee during the past four years while their studies have been in progress, and my admiration of the spirit and determination with which they have coöperated in their attack upon this baffling problem. I have felt it a great privilege to have a part in the furtherance of this effort.

It is not for the layman like me to attempt an appraisal of the work of the Committee, but I am certain it will have added substantially to the sum of human knowledge about this disease. This volume, which summarizes and brings into orderly review much of the important work of the past and the results of the Committee's investigations, will I trust prove helpful to those who now or later may be working upon various phases of this difficult problem.

The war against disease in all its forms presents a stirring challenge and maintains a keen and never-failing interest. One of its satisfactions is that the battle line never retreats and, while progress may prove slow, each gain is held and forms the base for further advance. The more difficult the objective, the greater is the incentive for attack. Infantile paralysis, and the possibility of its prevention and cure, holds a peculiar appeal, especially to those who love children. Other similar problems, no less difficult, have in the end yielded to persistent and devoted research and the solution has been found. There is every reason to hope for a similar outcome in this undertaking and the universal rejoicing in this achievement will more than repay the labors of all those who have been privileged to have a part in it.

JEREMIAH MILBANK

*June, 1932*





## PREFACE

The study of infantile paralysis upon which our Committee has been engaged during the past four years, owes its inception, its form of organization, and its financial support to Jeremiah Milbank of New York City.

The genesis of the effort is of such interest as to be deserving of record in this volume. While Mr. Milbank had long been interested in the possibilities of medical research, it was the skilful surgical and medical care in a severe attack of mastoiditis followed by meningitis suffered by one of his children that awakened his desire to foster some piece of research work. With the memory of his child's suffering, and his own thankfulness over his recovery, it was but natural that he should first think of research in mastoiditis. This thought he brought to the attention of the medical authorities of one of the great life insurance companies of which he is a director.

There, after an exhaustive preliminary survey, Mr. Milbank was advised that it would be exceedingly difficult to prosecute a program of research upon diseases of the mastoid processes which would offer much promise of discoveries leading to a reduction in incidence, severity or mortality in these diseases.

It was then that Mr. Milbank turned his thought to infantile paralysis, which he felt was the most dreaded ailment of childhood. He first sought the advice of Dr. William H. Park and Dr. Joseph A. Blake as to what a layman might do to promote further study of the disease, and early in 1928, the two doctors named, together with Dr. Milton J. Rosenau, Dr. Frederick P. Gay and Dr. Frederick Tilney had a number of discussions with Mr. Milbank as to ways in which interest in the various phases of the disease might be quickened and further research fostered and organized.

Several plans were discussed and discarded before the organization of the effort was finally decided upon. One idea to which considerable attention was given was that of offering an annual prize or prizes for important discoveries over a given term of years. Another was that of organizing and financing a new research body solely for the prosecution of the proposed study. All the thought given these two plans led to the conclusion that in all likelihood most of those best qualified to carry on

and direct the study were already associated with research centers in certain universities and laboratories, and that in these existing centers would be found the essential background of experience, the sources of advice and inspiration in related fields of investigation and the required technical skill and equipment.

The considerations thus briefly indicated led to the decision to have the study conducted by a committee to be named the International Committee for the Study of Infantile Paralysis, with a membership composed of the heads of the medical departments of a number of universities and laboratories here and abroad, each of whom would be free to choose those phases of the problem in which he was most interested, but all coöperating in an effort to have the sum of their work broadly inclusive of the whole field of research in this disease.

Mr. Milbank's undertaking in the financial sense then became that of providing funds needed in each of the research centers for the services of such assistants as might be added to their regular staffs, for any needed apparatus and for animals for experimental purposes. These expenses for the three-year period tentatively fixed as the duration of the study, were estimated to amount to about \$250,000 and Mr. Milbank agreed to provide the Committee with that amount.

The International Committee for the Study of Infantile Paralysis was then organized in April, 1928. Toward the end of the three-year period the Committee felt that it would be desirable to continue to some extent the effort for an additional year so as to bring to completion work already begun and also to prepare the general report on all the important investigations which have been made concerning the disease and its virus which is found in this volume, and to these ends Mr. Milbank gave an additional sum of \$30,000 making his total contribution \$280,000.

This Committee and all those who have coöperated in this study have a feeling of gratitude to Mr. Milbank for more than this generous gift of money to the cause of science. His continued and sympathetic interest in the project since its inception, his wise counsel at every turn, his ready appreciation of the difficulties which have beset the Committee in their research effort, all have been inspiring and a fine example of the way in which the layman may help the scientist in the battle against disease.

The membership of the Committee as originally organized was as follows: Dr. William H. Park, *chairman*, New York University; Dr. Joseph A. Blake, *vice-chairman*, New York City; Sir Charles Martin,



The Lister Institute, London; Dr. Edwin O. Jordan, Dr. Ludvig Hektoen, Chicago University; Dr. Frederick P. Gay, Dr. Frederick Tilney, Columbia University; Dr. Milton J. Rosenau, Dr. Hans Zinsser, Harvard University; Dr. Lee K. Frankel, Metropolitan Life Insurance Company, New York City; Samuel M. Greer, *Treasurer*, New York City; Dr. Josephine B. Neal, *Secretary*, Columbia University. Dr. W. Lloyd Aycock, Harvard University, and Dr. E. V. Cowdry, Washington University, St. Louis, later became members, and Dr. Paul F. Clark, University of Wisconsin, and Dr. E. W. Schultz, Stanford University, associate members. Dr. J. C. C. Ledingham, London, was appointed on January 1, 1931, to succeed Dr. Martin, who resigned. The death of Dr. Frankel in the summer of 1931 was deeply regretted by the Committee.

This, so far as is known to the Committee, is one of a very few instances where a piece of research work has been organized in this manner and from the experience of the past four years the members of the Committee feel that there is much to be said in favor of the plan. Certainly in this case all members of the Committee feel there was added inspiration in the thought of the joint attack on the problem and there was no one on the Committee, however keen his natural interest in the disease, who did not to some extent feel something of the stimulus of the competition which naturally followed from the association of these independent research centers in this special project. The Committee made no attempt at definite allocation of phases of the problem to the various members, nor did it seek to prevent duplication of effort; it was rather decided that it would be better to give the imagination of each member of the Committee its full play and that where there was duplication of effort, that would serve the very valuable purpose of checking findings and increasing their validity. The members of the Committee were kept informed of the character of the work being done by the different groups.

Much of the work on the disease undertaken by members of the Committee has appeared in the form of papers and articles in the medical press. These papers are starred in the bibliography. Some indication of the breadth of the effort will be afforded from the statement that there have been about eighty such papers or articles in the past four years. All articles upon the subject of poliomyelitis available in literature have been looked up and where they presented anything new or were of importance for other reasons such as in adding confirmation of earlier work, they have been consulted and utilized in the preparation of this volume.

The bibliographical studies covering some 8000 references, the selection of the more important papers, and the arrangement of this material for orderly inclusion in this volume represents a large task. This work has been conducted under the leadership of Dr. Helen Harrington, to whose devoted and expert service the Committee pays grateful tribute. Associated with her in the arduous task have been Dr. Mildred W. Wells and Miss Elisabeth F. Hutchin. They have had the difficult problem of deciding what to select for abstracting from the enormous number of articles which have been published. The Committee realizes that it owes a great debt of gratitude to Dr. Harrington for the successful completion of the task. This would have been impossible without her untiring direction and skilful guidance. One of the members of the Committee, Dr. Josephine B. Neal, the Secretary, has given unstintingly of her thought and time in aiding Dr. Harrington in the preparation of this volume. Dr. Neal has also written the chapters on Symptomatology and Treatment. The staff and the committee feel that without her interest and inspiration the work could not have been successfully accomplished. The Committee wishes to express its appreciation of the valuable aid given by Dr. E. S. Godfrey, Dr. Hubert S. Howe, and Dr. Lewis Dunbar Stevenson for suggestions and criticisms. Each chapter in the book has been read by one or more members of the Committee. Finally, the Committee wishes to express its gratitude to the Director of the New York Academy of Medicine, and to the Librarian, and to members of the library staff for their interest and help in the preparation of this book, and to Mrs. Cecile Hulse Matschat for editing and seeing the galleys through the press.

WILLIAM H. PARK, *Chairman*



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# CHAPTER I

## HISTORICAL SUMMARY

### ANCIENT RECORDS

The disease popularly known as infantile paralysis has ever since its recognition raised problems toward which diametrically opposed attitudes might reasonably be maintained. For some students it holds the position of a relatively new disease, such as encephalitis or whooping cough (Ruhräh and Mayer, R 58); while for others it has left visible traces in the records of the earliest human history and perhaps in pre-history. It may even belong among such scourges as influenza, which have prevailed at times during the past and then vanished for a period. However this may be, the admitted fact of its steadily increasing world-incidence, the nature of its toll, and its baffling epidemiological traits, give it present claim to considerable practical significance (L 17).

In the light of recent archeological discoveries certain possible very early cases have been studied retrospectively. Although data are of course lacking to furnish ground for reliable differential diagnosis in these instances, some of them appear of sufficient interest to justify consideration.

The Archeological Museum of the University of Pennsylvania contains a skeleton, dating from about 3700 B.C., found in a village south of Cairo by Flinders Petrie, who noted that one leg was shorter than the other and assumed that the thigh had been broken. J. K. Mitchell (1900, M 38), after making careful measurements of the bones of the skeleton, found no evidence of this. "One notices at once," he observes, "that the left leg is considerably shorter than the right, and at first sight the femur of the left side seems heavier and thicker than the right one. Measurement, however, makes it evident that the left femur's apparent greater circumference is only due to its shortening and to the strongly marked ridges at the site of the muscular attachments, which suggest that the muscles may have even been hypertrophied on that side. With this exception the left femur is imperfectly developed in all directions. The left femur is 8.2 cm. shorter than the right, round the middle of its shaft it is 1.2 cm. less; the neck is .4 cm. less in circumference. Condylloid measurements could not be compared,



as the left condyles are somewhat crumbled. The necks of the femora are the same length on both sides. There is no sign of fracture or injury to the bone of the left thigh."

After letting his fancy picture the patient possibly wearing a high-heeled sandal to compensate for the shortening, thus avoiding the spinal curvature to be expected in a man "who had come to old age with one leg three inches shorter than the other," he adds:

"The impossibility of cross-examination of the patient on his early history leaves us free to conjecture as to the cause of the difficulty, but nothing seems so probable as that the defect of growth is due to an attack of poliomyelitis, perhaps even an intra-uterine one. . . . The subject is one for larger discussion and study—and I have been concerned with the presentation only of what is, if my supposition of the causation is correct, the earliest known case of infantile palsy. . . ."

Although Mitchell's account has been cited in support of the view that poliomyelitis probably occurred in the earliest times, the author himself would doubtless grant to some of his critics that in the absence of other evidence of poliomyelitis than the shortening of the femur "the disease might equally have been of congenital origin" (MacAusland, M 1).

The suggestion that the lameness of Jonathan's son may have been due to poliomyelitis is sometimes met. Citation of the biblical passage in point (II Samuel 4: 4) will, however, permit the reader to form his own judgment as to the improbability of this: "And Jonathan, Saul's son, had a son that was lame of his feet. He was five years old when the tidings came of Saul and Jonathan out of Jezreel, and his nurse took him up, and fled: and it came to pass, as she made haste to flee, that he fell, and became lame. And his name was Mephibosheth." It is probable that trauma accounts for many of the cases of so-called infantile paralysis that have received historical or literary reference.

The paleopathology of Egypt has yielded a curious monument. The delineations on an Egyptian stele (see frontispiece) of the eighteenth dynasty (1580–1350 B.C.), now in the Carlsberg Glyptothek at Copenhagen, have been analyzed in detail by the physician and student of ancient Egyptian art, Ove Hamburger (H 6). His article has been translated by Ejnar Hansen (H 8).

After a brief description of the three figures on the stele—a priest, Ruma, of the temple of Astarte in Memphis, a woman, and a child—he continues: "When you look closely you will see that the figures are cut very distinctly by the artist, with precision and delicacy, but also that there is something wrong with the man's leg.

“Of course this abnormality has been noticed, and in the catalogue you read: *The drawing is not especially good. The man's one foot and leg is absolutely deformed; the 'stele' is possibly from a later period, when the Egyptian art was decadent.* If the aforequoted Egyptologist had been a physician, he would surely not have made that statement. In this case there is undoubtedly no misdrawing. The artist has produced a man with a ‘withered’ leg. The foot is in the typical *Equinus-position*. The slight flexion of the hip and knee joints is not enough to raise the heel so high from the ground. There is a shortening of femur, tibia and fibula. The whole leg is diminished in size. Another thing that speaks for the correctness of the drawing is the way *Ruma* is carrying his staff. It is originally the kind of cane Egyptians of quality used to carry, but in old pictures we always see them carrying it in front of them and parallel with the body. *Ruma* is carrying his cane in an unusual way, crosswise from the shoulder, in the bend of the elbow and alongside the withered leg, apparently as a support. If the artist has drawn the man as he was in life, it seems natural to think of either infantile paralysis or coxitis as being the cause of the deformity, and of these two infantile paralysis seems the most probable.”

In commenting on the frequent reference to this monument as evidence of the early occurrence of poliomyelitis, Ruhräh (R 58a) reminds us that the deformity “might, however, be due to some other lesion in the nervous system or to a disease of the hip joint contracted in infancy.”

These conjectural cases of poliomyelitis are cited not as mere historical curiosities, but because the antiquity of the disease has an important bearing on its epidemiology.

The epidemiological significance has possibly also been the source of the interest in Hippocrates' account of a winter epidemic of paralysis on the island of Thasos (Hippocrates, H 24). He tells us that, after a summer of severe and continued droughts and an autumn of heavy rains, “during winter, paraplegia set in, and attacked many, and some died speedily; and otherwise the disease prevailed much in epidemical form, but persons remained free from all other diseases.”

An archeological discovery that has stirred medical interest was made in 1921 near Ikigait in South Greenland. Some ruins of a medieval Norse colony, Herjolfsnes, had previously been located in this vicinity, and their examination was the objective of a Danish expedition in 1921. Excavation in the cemetery yielded about 25 skeletons belonging to the now extinct Norse population of Greenland, and dating, by the costumes, from the beginning of the fifteenth century (Poul Nörlund, 1924, N 31). In studying these skeletons, Hansen (H 9) found that



“a striking number of the individuals examined [6 out of the 25] have had diseases involving physical deformities,” such as weakening of one arm or one leg, asymmetry, scoliosis, tuberculosis of the vertebral column, pelvic defects, and slighter rachitic conditions on which the more grave deformities were perhaps superposed. One of them had “an asymmetrical scoliotic pelvis and marked kypho-scoliosis and must have had some atrophy of the muscles of the left inferior extremity;” another had “a pronounced atrophy of the left shoulder skeleton and muscles, besides wry-neck (*torticollis sin.*);” scoliosis of vertebral column and thorax occur in another; and still another “had the left inferior extremity, femur and patella much thinner and smaller than the right. Perhaps a scoliosis (an infantile paralysis is less probable) has also in this case been contributory.” In yet another there was a “pronounced cubitus valgus deformity, . . . of both elbow-joints, which was especially due to changes in the position of the fore-arms in relation to the upper arms.”

Aycock has stated his belief that such bony deformities in the Herjolfsnes skeletons are very probably due to poliomyelitis in childhood (Aycock, A 36).

In addition to sculpture and anthropology, painting has made its contribution to the meager fund of data that precede the historical accounts of poliomyelitis through some of the pathological delineations of the fifteenth and succeeding centuries. The passion for representations of the abnormal that culminated in the seventeenth century leaves us in no doubt regarding the high proportion of the maimed, halt, blind, and imbecile in the population of this period. Hieronymus Bosch and Pieter Breughel the Younger especially depict the gaits and deformities of the amputated and paralytic (F. H. Garrison, G 2). Some of the paralytic gaits represented in “The Procession of Cripples” of Bosch are considered to be probable poliomyelitic aftermaths.

## DEVELOPMENT OF MODERN CONCEPTION OF POLIOMYELITIS

### Period of Clinical Observation, 1784–1907

The eighteenth century references to reputed poliomyelitis, either literary or medical, need but the briefest consideration.

Vague and slight allusions in historical or medical annals to conditions which suggest poliomyelitis, especially those occurring in notable figures, have frequently led to more definite interpretation than their substance warrants.

The frequently cited case of the young Duc de Maine, son of Louis XIV, is an illustration in point. This can be definitely dismissed as poliomyelitis from statements in the Letters of Madame de Maintenon (M 14), quoted by Ager (A 9) as conclusive evidence "that the little prince had a chronic infection of some kind, probably a tubercular hip."

In the same paper on the early history of infantile paralysis Ager renders the service of dismissing as negative several works, chiefly of the eighteenth century, which are occasionally mentioned as containing probable references to poliomyelitis. Among these are the volumes of Bonetus, in 1700 (B 19) who reports histories of convulsions and loss of motion during teething, but describes additional symptoms which exclude the diagnosis of poliomyelitis; the 1746 volume of the Memoirs of the French Royal Academy of Sciences (H 27) which contains a reference to a form of migratory and recurrent paralysis; of Boerhaave, in 1761 (B 17), whose only statement that might bear on the point in question is, that reports have reached him of the rather frequent occurrence in some parts of Asia of a curious type of paralysis believed to be due to cold; of Portal, in 1803, who discusses cord lesions at some length in his pathological anatomy (P 23), but mentions nothing suggesting poliomyelitis; and of Baumes (B 8) whose detailed study of convulsions in infancy is equally negative.

Boerhaave's (B 17) reference to paralysis in Asia acquires increased interest when compared with Shaw's mention in 1823 (S 34) of its occurrence in India and with Goodeve's much later reference (1879) to frequent, although slight, paralytic illnesses among English children in India. In several other countries, clinicians encountered in practice cases which show more or less resemblance to the characteristic poliomyelitic syndrome. Among these may be mentioned, in England, Underwood (U 2), Shaw (S 34), Abercrombie (A 1) and John Badham (B 1); in Germany, Jörg (J 9); in Italy, Monteggia (M 42).

The very common attribution of the earliest recognition of the disease to Underwood in 1784 is perhaps due in part to the fact that the first edition of Underwood's treatise appeared in this year, and that little care was taken in distinguishing between the substance of the first and of the later editions; and in part to West's (W 15) mention of Underwood as the first to describe it, which was quoted by Rilliet and Barthez (R 16; R 17) and through them became the accepted belief on the continent.

The passage on the basis of which Underwood is usually credited with



the first description is quoted from the edition of 1793. Under the title of "Debility of the Lower Extremities," he writes:

"The disorder intended here is not noticed by any medical writer within the compass of my reading, or is not so described as to ascertain the disease. It is not a common disorder, I believe, and seems to occur seldomer in London than in some other parts. Nor am I enough acquainted with it to be fully satisfied, either in regard to the true cause, or seat of the disease, either from my own observation, or that of others; and I have myself never had opportunity of examining the body of any child who has died of this complaint. I shall, therefore, only describe its symptoms, and mention the several means attempted for its cure, in order to induce other practitioners to pay attention to it.

"It seems to arise from debility, and usually attacks children previously reduced by fever; seldom those under one, or more than four or five years old. It is a chronical complaint, and not attended with any affection of the urinary bladder, nor with pain, fever, nor any manifest disease; so that the first thing observed is a debility of the lower extremities, which gradually become more infirm, and after a few weeks are unable to support the body."

Then follows an account of the treatment used, after which he continues:

"When only one of the lower extremities has been affected, the above means, in two instances out of five or six, entirely removed the complaint; but when both have been paralytic, nothing has seemed to do any good but irons to the legs, for the support of the limbs, and enabling the patient to walk. At the end of four or five years, some have by this means got better, in proportion as they have acquired general strength; but even some of these have been disposed to fall afterwards into pulmonary consumption, where the debility has not been entirely removed. On this account, it may be suspected that the complaint is sometimes owing to scrofula; and I have been very lately informed by a gentleman of character, that he has seen one instance of a paralysis, or debility of this kind, in which, upon opening the body after death, the internal surface of the lower vertebrae lumborum was found carious, though there was no abscess of the psoas muscle, nor external tumor on the back, or loins.

"I have seen a similar debility seize grown people, especially women, after some very long illness, and has continued a year or more; during which time they were utterly incapable of walking without the help of crutches. These cases, however, have always been attended with

great pain in the commencement of the complaint, though without tumour of the limbs; and have seemed to be benefited by the external use of the waters at Bath."

This section has been rewritten in the 1799 edition, but the few verbal changes made are unimportant. Opinion is divided regarding the significance of the account, some authors believing that it quite fails to constitute a description of poliomyelitis (Seeligmüller, S 26; Medin, 1896, M 33; Gasparini, 1875, G 3; Römer, 1911, R 25; Ager, 1918, A 9) and in fact when considered as a whole gives a rather clear account of another disease—tuberculosis of the vertebrae and hip (Ager, A 9); while others, admitting that Underwood obviously failed to appreciate the cause of the condition, none the less think his cases in all probability instances of poliomyelitis (Ruhräh and Mayer, 1917, R 58; MacAusland, 1927, M 1).

The fourth English edition, of 1799, includes an added section on "Paralysis, or Palsy," which is of interest both because it contains paragraphs which seem to constitute a clearer picture of poliomyelitis than Underwood had in 1793; and also because it again, when read in its entirety, discloses the confusion existing at this period among paralytic conditions which are today so readily differentiated. In this section he writes:

"The Palsy is a more common disorder in infants, and young children than writers seem to have imagined, being confined to no age (having been seen as early as the third day after birth), and attacking children in very different degrees, in the manner it does adult persons. It, accordingly, sometimes seizes the upper, and sometimes the lower, extremities; in some instances, it takes away the entire use of the limbs it has attacked, and in others, only weakens them. Sometimes the speech is very much affected, and at others not at all; the intellect is also greatly impaired in some instances, and in others is only torpid; for though children may be dull and heavy, like other paralytics, yet when roused, their imagination is found to be fully awake to the common objects around them.

"The palsy more commonly appears in the form of hemiplegia; but if it be neither fatal, nor soon cured, it is often found to steal imperceptibly upon the other side of the body. In one instance, I was witness to the paralytic affection quitting one side, to seize the other, only two days before the child died.

"In any case, the palsy in young subjects is to be treated in much the same manner as in adults; and being usually attended with costiveness,



calls for brisk purges in the first instance, and a repetition of opening medicines throughout the course of the complaint. And, indeed, if cathartics and blisters do not soon afford relief, the disorder usually becomes chronic, and the child sinks gradually in the course of a few months, or drags on a miserable life for ten or twelve years, with more or less debility of the arms or legs; but very rarely arrives at manhood. Indeed, the causes of palsy, particularly in young people, who are still growing, are so numerous, and are often so entirely out of the reach of art, as well from their nature, as their seat, being frequently in the nerves themselves, or the brain, that such an event cannot be wondered at, and the effect they produce on the spine, or on the limbs.

“But where no morbid change of parts has taken place, perhaps infants and young children are oftener perfectly cured than those more advanced in years, by the mere exhibition of two or three brisk purges, whereof calomel often forms a necessary part, as the palsy frequently originates from foul matters in the first passages. . . .

“I have noticed a few instances of a partial paralysis of one, or all the extremities; but this has always given way very soon. Besides teething infants, whom it has been said to attack, I have seen it in others who are older, and the finest children, and is then generally attended with a foul state of the bowels. In any case, the only remedies I have found necessary, have been calomel or some other purgative; sometimes an emetic, and volatile embrocation to the limbs. Electricity, I am told, has been advised in one instance; and if the complaint should not otherwise yield, may as properly be had recourse to in this, as the former instances.”

In 1823 Shaw included in his quaint little volume on the “Nature and Treatment of the Distortion to Which the Bones of the Spine and Chest Are Subject” (Shaw, 1823, S 34) a chapter entitled “Enquiry into the Causes of the Partial Paralysis and Wasting of One of the Limbs during Infancy, Which Frequently Produce Distortion of the Spine.” He states that “there is much variety in such paralytic affections, but to the greater proportion, two circumstances seem to be common; viz. their connection or dependence on the state of the bowels, and the effect they produce on the spine, or on the limbs.

“The species of paralysis most interesting in relation to distortion of the spine, is that which is marked by a wasting or deficiency in the growth of a particular part, although unaccompanied with much defect, either in the power of sensation, or of motion.” After citing two cases, he continues: “In several cases nearly similar, the change in the charac-

ter of the limb became evident, so soon after an attack of abdominal irritation, as to leave little doubt of the cause. But, in the greater number of such cases, the defect is seldom observed at the time of the first influence, and does not become evident until the other parts of the body are fully developed. In consequence of this, it is often difficult to trace these affections to their origin, and we are occasionally unable to determine whether they proceed directly from a certain condition of the bowels, or from a disease of the brain. . . .

“But certain paralytic affections of the muscles are sometimes so instantaneous, that we must consider them as depending on a change which has suddenly taken place in the brain, or spinal marrow, or in the nerves which supply the affected parts. These cases differ from the former, in being generally accompanied with an immediate loss of voluntary power over the affected muscles. . . . I have been told that such sudden attacks are common among children in India and that strong and healthy children are more frequently affected than those of a weakly constitution.”

Shaw also refers to a patient under his treatment who, during his childhood in India, had lost power over one leg in the course of a single night. His parents said that he had been in good health at that time. This statement has led to the suggestion that the disease is perhaps of Asiatic origin, or was at least known very early in India, and probably brought to England by returning Anglo-Indians and thence carried to the continent (Ager, A 9).

Much more important from several standpoints than the preceding accounts is the report by Badham (B 1) on 4 cases which occurred during the summer of 1835 in the small community of Worksop, England. In addition to their intrinsic value as clinical descriptions—as the first generally unquestioned observations of poliomyelitis in British medical literature—they form the earliest *group* of cases known to occur within small area and brief time; and last, but by no means least, they furnished Heine with the incentive to study in more detail this strange form of paralysis in children. Badham’s report is quoted at length:

“Case I.—Ann Hare, aged 2 years, was brought to me by her mother, on the 14th of August, with paralysis of the right leg. Her account of this seizure was as follows:—

“The child had enjoyed uninterrupted health to the evening of her attack, with the exception (if, indeed, it can be so called) of slightly augmented thirst and some drowsiness, now remembered by the mother to have preceded the seizure by two days. On the evening of the



13th the child was put to bed, having run about and amused herself as usual during the day. On the following morning her mother's attention was first attracted, in dressing her, to an unusual appearance of the eyes, which, as she said, appeared to be turned inwards. A new cause of apprehension presented itself in putting the child on her feet, when it was found she could not stand. Medical advice being immediately sought for, it was thought sufficient, I understand, to keep the bowels open and to employ a warm bath. No advantage, however, being procured under this treatment, she was brought to me on the 14th; a week after her attack. Her *appearance* at this time did not denote *any* disease—she was playing in her mother's lap; but on accurately examining the two limbs, it was found that *motion* in the right was completely destroyed, and in the left somewhat diminished; while *sensation*, perfect in the left limb, was impaired, without being suspended, in the other. At this period there was neither wasting of the limb nor diminution of temperature. Strabismus very decided; the pupil drawn to the inner canthus, and the eye-ball fixed there, as I found in attempting to direct the vision outwards, and the pupil on the same side as the palsied limb was dilated. No disturbance of constitution could be traced from teething, or from torpor of the bowels; nor, on examining the spine attentively, could I detect any tenderness on pressure.

“I directed calomel in repeated doses, cold applications to the head, blisters to the spine, and cataplasms to the affected limb. Under this treatment the drowsiness was removed in five days. On the fourth, indeed, from its adoption, the ball of the right eye became suddenly liberated from its constrained position; the other eye recovered more slowly, a few days afterwards. The limb now shows (on the 15th of October) some return of sensibility, but the temperature is considerably below that of the other, and loss of substance has proceeded to a considerable extent. The exercise of the will over the affected extremity, though entirely abolished at first, has now partially returned, inasmuch as she no longer drags the limb after her, as she at first did, but projects or flings it forward with a jerk, the direction and force of which she seems not to have the slightest power to moderate or control.

“Case II.—My second case singularly occurred a few days afterwards; its subject, a little girl, also 2 years old, who had been seized a week previously to my seeing her, with an equally sudden loss of the same extremity; which took place also during sleep, without any prior intimation. Thirst, remarked also in the former case, was a more promi-

nent symptom in this; and the mother thinks there may have been somewhat more drowsiness about the child than common. The pupil of the left eye was dilated; the eyeballs free in their sockets; and, indeed, this unimpaired mobility constituted the only marked difference between the two cases. This case was chiefly treated with strychnine externally applied, but without any benefit; nor did stimulating embrocations and mercurials meet with better success. The perfect contractility of the pupil was soon recovered, but the limb remains perfectly palsied and useless, though sensation has been somewhat restored.

“Case III.—My attention has been a third time arrested by a case analogous in all its material points to the two just cited, except that the paralysis here is of the *upper* extremity. The patient, a girl, aged 2 years and some months, without any previous fit or other appreciable cause, was found one morning to have lost the use, and a great portion of the sensibility, of the left arm, which was swollen throughout its extent, the right arm being also implicated, though to a very inconsiderable degree. The right pupil is much dilated, the left is contracted; the evacuations from the bowels have been dark and offensive. No tender spot can be perceived on the spine; all the functions are healthy.

“This case was also treated with strychnine, preceded by smart purgatives of calomel, &c., and with no better success than the last. The limb is now, after the lapse of nearly two months, hopelessly paralyzed, and swings like a suspended object attached to the body.

“Case IV.—John Hollis, a little boy of 2 years and a half, was lately seized with exactly similar symptoms to those above described. The action of the left lower extremity entirely lost, sensation much diminished; the temperature of the affected limb is diminished, and it is somewhat reduced in size, the muscles being more flabby than those of the other limb.”

These cases Badham frankly admits puzzled him—both as to diagnosis and also as to treatment. He has singled out for special comment, as common to all four cases the following points:

“1. The extraordinary youth of the patients is to be noticed. It will be observed that the age in all the above cases corresponded within a few months.

“2. Although each case was either preceded by or ushered in by some apparent cerebral symptoms—viz. in two by drowsiness, in the others by an abnormal state of the pupil—yet

“3. It is remarkable that in no one instance has the health been in any degree impaired.



"4. If the case in which the remarkable strabismus occurred should lead us to suspect a cerebral complication, rather than a spinal one, there is other suspicion of congested, oppressed, or irritated brain.

"The above cases (of which the first was seen some time ago by Dr. Outram, and three of the four subsequently by my father, Professor Badham), may probably suggest analogous ones in the experience of some few of your readers, who may also be able to help me to a treatment from experience; for we know nothing of the intimate character of any species of palsy, so as to manage it philosophically, and to adopt a medication without a defined object. A view which admits of being stated in intelligible language, is scarcely medicine. Some would doubtless in these cases recommend issues; some would counsel electricity; others would put me in mind of Arnica, or other *soi-disant* remedies for palsy; but I am unwilling to disturb the digestive and nutritive functions in such young subjects, and would rather count on these important processes as my auxiliaries, than venture on equivocal remedies which may, or rather must, depress them. I shall be thankful, for any suggestion; for it is lamentable indeed to witness one of the most humiliating infirmities of age inflicted on infancy! Perhaps one may reasonably expect some of the little patients to outgrow their disastrous condition, unless it shall be concluded that palsy in such instances is only an unusual and early evidence of deeply latent cerebral mischief."

The interest in Badham's reports lies not only in the cases themselves, but in the challenge they offered that fixed the attention of Heine upon the problem presented.

In Germany a case of the development of clubbed feet following a long illness was reported in 1810 by the pediatrician, Jörg (J 9), a medical associate of the elder Jacob Heine.

This case has been mentioned as the very earliest of the indubitable accounts of poliomyelitis (Römer, R 25), but it is grouped by some (Ruräh and Mayer, MacAusland) among the "rather vague paralytic conditions" described also by a few other German workers. The essential features of the case were the occurrence of a febrile attack which lasted "a long time" and the mother's later observation that the child "did not use its feet properly" which later became clubbed. Reference to this report, which is quoted in full in the *Chapter on Symptomatology*, will permit the reader to make his own interpretation.

Gasparini (G 3) discovered an interesting clinical report in the writings of the Italian surgeon, Monteggia (M 42). In the edition

which contains notes by Caimi (Milan, Truffi, 1829–1830) the following passages appear:

“In this connection I shall mention a special kind of paralysis, limited to either of the legs, which I have several times seen in my practice but which is not yet found in books. It affects sucklings or children not much older ;they begin by suffering a fever for two or three days, then it is discovered that one of their legs is rendered immobile, flaccid, weak, paralytic, save when certain ones exhibit a slight movement when the sole of the foot is tickled. The fever soon goes away and the child feels well; but the member remains motionless and as time goes on regains only an imperfect degree of strength, to such an extent that I know persons who are now adults who still drag one weak leg because they were not treated in time.

“Likewise it is not unusual for the disease to affect both lower extremities simultaneously, but this state does not last long, for in one or two days the paralysis affects a single leg.

“I am not very certain as to the cause of this disease; but the fact that I have observed that it usually accompanies fever, and the fact that I have recently seen it accompanied by symptoms of dysentery in one child make me suspect that it comes from colic, or rather from a rheumatic affection.”

The history of poliomyelitis as recorded in medical literature is linked to a few outstanding names, preëminent among them those of Heine, Medin, and Wickman. The several accounts that have been quoted seem to contain the clearest descriptions of symptoms of poliomyelitis recorded in the literature before the year 1840—the first landmark in its century. In this year appeared the first edition of the first monograph ever published on the disease we are considering. This was the outcome of the systematic studies of Jacob Heine of Cannstaat (H 18), made after the reading of Badham’s cases had focussed his attention on a special type of flaccid paralyses which he had seen in his clinic.

Heine belonged to a family of skilled orthopedists and mechanics, and his first interest had been in the mechanical problem of devising exercising machines for development of weakened muscles, improved forms of braces and supports, in general, in the field of corrective treatment. His keen clinical insight, however, led him on to the effort to systematize the varied paralyses that he was continually seeing, to speculate on the etiology, and, without any positive necropsy findings



at all, to suggest the probable pathological basis which later microscopic studies were substantially to confirm.

The following has been taken freely from Heine's 1840 monograph. The features noted as "prominent in almost every case" were:

- (1) The age of the patient (6 to 36 months).
- (2) The good general health preceding the illness and the strong and "blooming" bodily constitution of the patients.
- (3) The congestive, febrile, irritative and convulsive manifestations which, in the majority of cases precede the paralysis.
- (4) Pain—recognized in small children by their crying.
- (5) The fact that, in most of the cases the first result of the affection was paralysis of both lower extremities, and that there were almost no cerebral symptoms.

Heine concluded that these symptoms "point to an affection of the central nervous system, namely of the cord, of an irritative and congestive sort." The paralysis was attributed to an exudate in the spinal canal. The transitory nature of the paralysis in the arms, the back, or even in one of the lower extremities was thought to be either because of a "consensual" relationship between the different regions of the spinal cord, or because of a less extensive and intensive congestion and irritation of the upper spinal axis or because the fluid exudate was soon re-absorbed from the upper portions of the spinal canal while it persisted in the lower portion. According to the laws of gravity, the serous exudate should exert as much pressure on the posterior as on the anterior nerve roots. Heine therefore resorted to the further assumption that the anterior columns are affected by a more solid lymphatic exudate, while the posterior were soon relieved by resorption of the more fluid exudate.

In contrast to Heine's positive contribution the period between the publication of his two monographs may be said to be characterized by negative findings. Although isolated cases, or small groups were observed and reported in several different countries, very little was added to the understanding of the nature of this illness.

The conception of the disease held by an author was often reflected in the name by which he designated the affection he was describing. Thus Kennedy (K 8; K 9) observed that in certain instances the paralysis disappeared promptly and cure was complete; such cases he classified as "the temporary paralysis of early life." Kennedy believed that there was usually no organic lesion and regretted the tendency of the day to relate nerve diseases with paralysis to some change or other of the brain or cord.

The term "morning paralysis" was used by West (W 15) because he had observed instances in which paralysis was discovered in the morning although the child had apparently been in perfect health the night before. Kennedy also had commented "that the paralysis is, frequently at least, observed for the first time on taking the child up" and felt "that it is often caused by the child lying on the limb while in the cradle."

Like Kennedy, Richard de Nancy (1849, R 14) and Rilliet and Barthez (1851, R 17) in France opposed Heine's hypothesis of a spinal origin of the disease. The term "essential infantile paralysis" originated with Rilliet and Barthez and was based upon their repeated negative results at autopsy.

Still another name was employed by Duchenne of Boulogne (1855, D 25), "*Paralysie atrophique graisseuse de l'enfance*." In contrast to other authors of this period, Duchenne supported Heine's view. In cases of trauma to the cord, he had noted a relation between the paralyses, the muscular atrophy and the electrical reaction of degeneration; he believed, therefore, that these infantile paralyses might also be of spinal origin.

In the period following the second edition of Heine's monograph (1860), clinical contributions of varying importance were made by Seeligmüller, Strümpell, Pierre Marie, Medin, Caverly and Wickman.

Seeligmüller (1878-79, S 26) had opportunity to observe 75 cases in various stages of the disease and made detailed studies of the early symptoms, and of the distribution of the paralyses.

In 1884, Strümpell (S 65) "pointed out the resemblance between certain cases of acute encephalitis with spastic paralysis in children and cases of poliomyelitis. He concluded that these two types of disease of the central nervous system had a common etiological factor, and suggested for the first time the hypothesis that an external infectious agent was responsible for them" (P 7). His work not only added the description of a hitherto unrecognized type of the disease, but also brought out the idea that the causative agent might localize elsewhere than in the cord. The following year his observation was corroborated by Pierre Marie (M 16). The cerebral type is therefore often referred to as the Strümpell-Marie type.

In 1887 Medin (M 32) observed an outbreak of 44 cases of infantile paralysis in Stockholm. Prior to this year the disease had been infrequent, not only in Stockholm, but indeed in Sweden. During



Medin's experience of 15 years in the Polyclinic, he had seen 1 or 2 cases yearly. These were isolated cases, usually seen in the atrophic stage; but from May to November, 1887, there were 44 cases, 4 of which ended fatally, 3 of the patients dying of this disease, and 1 of a disease which Medin believed to be diphtheria.

The opportunity afforded to Medin to witness so large an outbreak made possible an important extension in the knowledge of the disease. Medin observed 27 cases of Heine's spinal type, but occurring at the same time were 17 cases which presented unusual symptoms as to localization. From the fact that these spinal and other forms occurred at the same time, and from his observations of the acute stage, Medin drew the conclusions: that infantile paralysis is an "acute infectious disease—an entity;" that it may appear epidemically; that not only are the gray anterior horns of the cord affected, but that in the acute stage, the whole organism is involved; that the onset may be interrupted by a period of fever-free remission; and that the symptom-complex changes according to the portion of the central nervous system most affected. Medin distinguished, in addition to the spinal type, the bulbar, ataxic, encephalitic, and polyneuritic types, but, "whether the disease shows itself as poliomyelitis, polyneuritis, as monoplegia, or as polio-encephalitis acuta, these differently localized forms belong genetically to one and the same disease."

Medin's important contributions to the knowledge of poliomyelitis entitled him to share with Heine the credit for the development of the clinical picture of the disease, and led Wickman to propose the name "Heine-Medin disease."

Caverly in 1894 (C 3; C 4; C 5) added a new and important type, the nonparalytic, to the list. He called attention also to the stiffness of neck and back muscles as an early and significant symptom.

Wickman extended and clarified Medin's concept of poliomyelitis. He recognized many cases of the abortive (including the nonparalytic) type, added the meningitic, and the type resembling Landry's paralysis, now usually considered a subdivision of the spinal type.

### Period of Pathological Investigation, 1863–1907

Less than fifty years elapsed from the time of the first positive microscopical examination of a case of poliomyelitis by Cornil in 1863 (C 27) until Wickman began his investigations in 1905 (W 20). During this period, however, a fairly complete picture of the pathological anatomy of the disease had been built up and theories were advanced

as to the point of entrance of the causal agent and the route by which it was spread through the body. These are problems that even now are not definitely solved.

A wealth of detail concerning the early autopsy findings and their interpretations is found in Jacobi's study of the pathogenesis of the disease (1874, 1886, J1, J1a).

The importance of Charcot's work (1870, C 10) lies not only in its relation to poliomyelitis but in conclusions fundamental to all neuropathology. Charcot recognized the significance of the relation between the lesions in the motor nerve cells of the anterior horns and the atrophy and loss of power in the corresponding muscles. He believed, too, that the motor nerve cells were the seat of the primary lesion. Roger and Damaschino (1871, R 32), on the other hand, found evidence of acute inflammation in the cord and suggested that vascular changes and cell proliferation might precede injury to the ganglion cells. In spite of all the advances of modern technic, these opposing views, though somewhat modified in form, still claim the attention of students of this disease.

At this early period, pathological alterations in the white matter were seldom observed; the belief that they were dealing with an affection of the gray substance of the cord led Kussmaul (1874) (cited by Frey, F 64, F 65) to employ the term, still in common usage, *poliomyelitis anterior acuta*.

The history of the pathology of the acute stage begins with the work of Rissler (1888, R 18). Rissler not only gave a comprehensive account of the lesions in the interstitial tissues and vessels of the cord but he was the first to describe destruction of the ganglion cells by phagocytosis. Rissler also noted softening and enlargement of the spleen, enlargement of the solitary follicles and Peyer's patches of the intestine, and of the mesenteric lymph nodes.

The vascular theory also was advanced at this period. Certain workers, Kawka (1889, K 5), Goldscheider (1893, G 13), Siemerling (1894, S 41), and others believed that the location of the lesions was determined not by cell groups but by the distribution of the blood vessels.

Bülow-Hansen and Harbitz (1898, B 38), like Rissler, observed important intestinal changes and made the suggestion that these might be evidence that the causal agent had gained entrance to the body through the gastro-intestinal tract, a belief held by many investigators at the present time.



The modern conception of the pathological anatomy, however, begins with the work of Wickman (1905-11, W 20; W 21). Wickman not only gave a comprehensive picture of the histopathology of the disease but also studied the problems of the aetiology of infection and of pathogenesis. Wickman also believed that infection took place by way of the alimentary canal; transmission of the virus was along the nerves by way of the lymphatics. One important point raised by Wickman had not previously been considered—why this disease with strictly localized pathological lesions should develop first clinically as a systemic disease.

Although experimental investigations have contributed enormously to a knowledge of the details of the pathological processes involved in poliomyelitis, it must be admitted that some of the most important questions raised by the pioneers of this early period have not yet been solved.

### Period of Epidemiological Interpretation, 1890-1907

No circumstance in the history of poliomyelitis is so baffling as its change, during the last two decades of the nineteenth century, from a sporadic to an epidemic disease. From the standpoint of its epidemiology, poliomyelitis is a disease of the present.

No satisfactory explanation of this change has been given. Römer writes on this point: "It is curious that the older literature contains not a single reference to any epidemic, although infantile paralysis most certainly occurred. After the appearance of Heine's monographs, and at a time when the literature of the disease was becoming extensive, no mention was made of any epidemic before 1880. It may have been because small groups of cases were not recognized as such, owing to the infectivity of the disease being unknown, or because the clinical differences between the cases caused them to be regarded as examples of different diseases. But when the symptomatology of the commonest type of the disease had been fully described under the name of spinal 'infantile paralysis,' the absence of reports of epidemics can be explained only by the fact *that such epidemics did not occur before 1880.*"

The various theories which have been advanced to account for this change have been briefly summarized in the *Chapter on Epidemiology*.

Badham's account of the 4 cases in Worksop, England, quoted earlier, is the first mention of a group of cases occurring within a brief interval in one small area.

George Colmer, in 1843 (C 22) also records what seems to have been a group of cases of poliomyelitis. His account is brief and is given in

full: "Whilst on a visit to the parish of West Feliciana, La., in the fall of 1841, my attention was called to a child about a year old, then slowly recovering from an attack of hemiplegia. The parents (who were people of intelligence and unquestionable veracity) told me that eight or ten other cases of either hemiplegia or paraplegia had occurred during the preceding three or four months within a few miles of their residence, all of which had either completely recovered, or were decidedly improving. The little sufferers were invariably under two years of age, and the cause seemed to be the same in all—namely, teething."

As to these cases which Colmer records, Lavinder, Freeman and Frost (L 16) conclude: "While in all likelihood this may have been a small epidemic of poliomyelitis, yet the entire lack of details and the character of the evidence presented render questionable its inclusion as a definitely established epidemic of the disease." If these cases were, indeed, cases of poliomyelitis, it is curious that so early an outbreak should have occurred so far South, where, even today, the disease seldom assumes epidemic proportions.

Lavinder, Freeman and Frost (L 16) credit Bull with having described the first authentic outbreak of poliomyelitis. They cite in support of this opinion Leegaard's account (B 39; L 26) of which they give a full translation. In 1868 Bull treated for what he thought to be acute spinal meningitis 14 patients, 5 of whom died. These cases had occurred in the Modum district of Norway, not far from Oslo, 1 in May, 4 in June, 8 in July, 1 in August. A reading of this account convinces one that Bull was dealing with true poliomyelitis.

Bull wrote: "It does not seem apparent in this small epidemic that contagion played any rôle, because the disease occurred here and there in different places of the district without the possibility of establishing any relation between the various cases or the families of the same. Yet I will state that in one court two children were taken sick at the same time. Moreover, in two places where cases occurred, the brother or sister in the same house sickened, but not with an evident spinal meningitis—rather with a light and unimportant form, so that the patient, after the course of a couple of days, was entirely well. Since, however, along with the symptomatology there occurred unimportant tearing pains in the neck, and since, furthermore, we have the occurrence of relationship to a case of the disease as well as the occurrence of a slight paralysis of the upper arm for half a day, I believe that I am able to say in this case that I was dealing with the beginning of the same affection which had previously been observed in the brother or



sister. I have observed two cases of this kind where the symptoms were unimportant. These are not included in the 14 cases reported."

It will be seen that, while Bull described the first real outbreak of poliomyelitis, he did not conclude from his evidence that the disease was contagious. While he recognized that connected cases had occurred, the impossibility of tracing direct contact among others led him to doubt the contagiousness of the disease.

Other authors, including Wickman (W 21) and Batten (B 7) cite as the first epidemic the one reported by Bergenholtz which occurred in Sweden in 1881. Our knowledge of Bergenholtz' observations is contained in a brief notice in Medin's article (M 32) which states that Bergenholtz reported before the Medicinal-Collegium a small epidemic of 13 cases occurring in Umea (about 64° latitude) in 1881, but that the report was never published. Since no data are, therefore, available upon which to base a critical opinion, it has apparently been the fact that Medin vouched for the authenticity of the outbreak which caused it to become so universally accepted.

Cordier (C 26) gathered detailed information on a group of 13 cases which had occurred in June and July, 1885, at Sainte-Foy-l'Argentière, near Lyon, data which he hopes will, "in showing that atrophic paralysis of childhood can occur in epidemics, also bring out the fact that this paralysis is a specific, infectious disease, perhaps microbic." Cordier inferred also that the disease was contagious, and was, so far as we are aware, the first to conclude on epidemiological grounds that poliomyelitis is a contagious disease.

Several clinicians, however, had previously reached a similar conclusion. Schreiber (S 11) says that to Landouzy belongs the distinction of first suggesting the infectious nature of myelopathies, and that this suggestion was made by Seeligmüller (1880, S 27) in the same year.

During the following years numerous other outbreaks of varying proportions were reported from widely scattered localities in many different countries.

The history of the epidemics has been given by Wickman (1907, W 21), Holt and Bartlett (1908, H 29), Job and Froment (1910, J 8), Batten (1911, B 6a), Low (1911, L 72), Römer (1911, R 25), Ruhräh and Mayer (1917, R 58), Lavinder, Freeman, and Frost (1918, L 16), MacAusland (1927, M 1), and others. Comparison of their lists reveals discrepancies that are not surprising in view of the fact that the early reports are not always available for first-hand study.

A consideration of the lists of epidemics given by the authors men-

tioned fails to support the suggestion sometimes met with that the epidemic of poliomyelitis which began in the Scandinavian peninsula in 1887 spread out in orderly progression to other countries. There were reported, for instance, 26 cases in Boston (1893) (Putnam and Taylor, P 30), 132 cases in Vermont (1894) (Caverly, C 6), 14 cases in Australia (1895) (Altman, A 10), 17 cases in Italy (1895) (Buccelli, B 37), 8 cases in Spain (1896) (Roset, R 54a), 15 cases in Alabama, U. S. A. (1896) (Bondurant, B 18), 11 cases in London (1879) (Buzzard, B 44), 15 cases in Germany (1898) (Auerbach, A 32), 42 cases in Vienna (1898) (Zappert, Z 1), 5 cases in Italy (1899) (Simonini, S 43), 55 cases in California, U. S. A. (1901) (Woods, W 29), and various others analogous to these. Not, however, until the startling outbreak in Norway and Sweden from 1903 to 1906, was any realization obtained of the dramatic proportions which the disease might on occasion assume.

Another point of interest that strikes one in studying the lists of early epidemics is the rather considerable number occurring in the warmer climates. The outbreaks reported by Colmer in Louisiana, 1843, and by Bondurant in Alabama in 1896, and the epidemics in Italy, form a larger proportion of the total cases than might be expected from the present geographic distribution.

The fundamental significance of Medin's work became fully apparent when Wickman, his pupil and successor, carried it to fruition. Wickman published in 1907 (W 21) his investigations of the 1025 cases which occurred in the great Swedish epidemic of 1905. He was able to verify and widen Medin's conception of a disease etiologically an entity. To Medin's observation that poliomyelitis was an infectious disease, occurring in epidemics, Wickman added a theory as to how the infection was spread; and to his theory that person to person contact was the mode of transmission, he brought a wealth of confirmatory evidence. In the *Section on Contact*, the circumstances under which Wickman worked have been mentioned. The lonely parishes of Sweden, the infrequent and hence readily recalled intercourse between the isolated farms, offered ideal conditions for a study of contagion. Wickman proved in many instances that direct contact between cases of the disease had occurred, and in others that indirect contact through healthy intermediaries had taken place. He also became convinced that mild and unrecognized cases played a large rôle in the spread of the infection.

Wickman's concept of the transmission of poliomyelitis is the one generally accepted by epidemiologists today. Contributions made since his studies have been largely in the nature of a verification of Wickman's theory.



### Period of Experimental Contribution, 1908 to the Present

With the publication of Wickman's monograph in 1907, three phases in the evolution of the modern conception of poliomyelitis attained a climax: the classic conception of a "spinal infantile paralysis" had expanded to include widely varying clinical manifestations; the pathological investigations had culminated in the first critical analysis of the pathogenesis; the epidemicity of the disease had been established, and the theory of its transmission by contact widely accepted.

Meanwhile, the sciences of bacteriology and immunology had been making great advances. It is not, however, to be wondered at that increase in knowledge of the etiology of poliomyelitis was slow. Study of the filterable viruses presents difficulties which, even with the aids of modern technique, are far from surmounted. The lack of a susceptible laboratory animal, and of an artificial medium upon which the virus could be cultivated, held back for many years an experimental approach to the disease.

It is an interesting coincidence that the year following the publication of Wickman's monograph should have marked the beginning of a new period. In 1908, Landsteiner and Popper (L 10), using as inoculum the cord and brain of a child who had died of poliomyelitis, were successful in conveying the disease to 2 monkeys. During the following year the transmission from one monkey to another—essential to show the multiplication of a living organism—was achieved by three independent groups of investigators.

With the discovery of a suitable laboratory animal, the present period of experimental research was inaugurated. Contributions to the etiology, immunology, and pathology of the disease have followed in quick succession, and have confirmed, on experimental grounds, Medin's concept of a "genetic entity," protean in its manifestation.

## CHAPTER II

### ETIOLOGY

#### INTRODUCTORY NOTE

"It would be presumptive on my part," Heine (H 18) wrote in 1840, "If I . . . should attempt to give a satisfactory explanation of the etiology" of this disease. The features prominent in almost every case, "point to an affection of the central nervous system, namely, of the cord, of an irritative and congestive sort." Heine noted that in one case an acute exanthematous disease had preceded the illness and believed, moreover, as did Colmer (1843, C 22) and Kennedy (1850, K 9) that teething might be at least a predisposing cause. Traumatism, over-exertion, exposure to cold, nervous shock, acute febrile diseases were also mentioned as the exciting causes by various authors (Chapin, C 8; Fischer, F 10; Galbraith, G 1; Seguin, S 28; Vogt, V 4).

In 1880, Professor Landouzy (cited by Schreiber, S 11) first suggested that myelopathies were infectious and Seeligmüller in the same year (S 27) made a comparison between poliomyelitis and infectious diseases, saying: "Because of this analogy . . . and in consideration of the fact that 'spinale Kinderlähmung' not infrequently develops with febrile manifestations after the manner of acute infectious diseases, one must have in mind that this disease may have a toxic cause."

Strümpell, however, in 1884 (S 66) was the first to formulate a definite hypothesis. He affirmed the infectious nature of a "group of diseases, which, both in their course and in certain of their symptoms, show a similarity with each other that cannot fail to be recognized: acute multiple neuritis, acute poliomyelitis and a still relatively little known form of acute encephalitis in children. All these diseases begin rather suddenly with an often considerable degree of fever. The patients are mentally dull, have headache, show gastric disturbances, sometimes a slight enlargement of the spleen, often, too, joint rheumatism and a slight albuminuria. According to the present views, these are all symptoms which point, undoubtedly, to an infection of the body with an organized toxin. . . . The idea seems to us worthy of consideration of grouping the above-named affections as an etiological entity and to look upon them as variously localized manifestations of the same, or at least of very closely related specific disease-agents."



Soon after, Pierre Marie (1885, M 16) was struck by the resemblance of infantile hemiplegias following infectious diseases to infantile paralysis and called attention to the fact that Strümpell had made this comparison between acute poliomyelitis and other infections.

## BACTERIOLOGY

### Early Bacteriological Investigations

**Negative Results.** In most of the early pathological studies, no mention is made of microorganisms. It can be assumed that, in spite of the painstaking microscopic examination made by these workers, none was demonstrated on section. Bülow-Hansen and Harbitz (1899, B 38), however, carried out an extended investigation while making a pathological study of 2 cases that died during the acute stage. Cover-glass preparations from the cord substance showed no bacteria by Gram or Loeffler's stain; numerous sections from various levels of the cord were negative for bacteria or bacterial emboli. Cultures of the cord substance, of the blood and of the spleen were sterile. Cultures of the spinal fluid were negative with the exception of one culture tube where a peculiar Gram-positive diplococcus or short double-rod was found but which showed no virulence for animals. Other animal experiments were also negative. This one positive finding was felt to be too isolated to have any significance in view of the numerous negative results.

Guinon and Rist (1903, G 20) found that spinal fluid cultures from 2 acute cases were sterile; smears made from the residue of the centrifuged fluid showed no bacteria; animal experiments were negative. Perkins and Dudgeon (1907, P 9) reported blood cultures made at autopsy, sterile; in their case, however, formalin had been injected into the spinal canal at death.

A larger series was studied by Wollstein (1908, W 28). Spinal fluid was obtained during life from 20 cases (reported also by Starr, S 54). Cultures, both aerobic and anaerobic, were sterile in 15 cases. Growth was observed in 5: in 1 a white staphylococcus was identified, in 1 a short Gram-positive bacillus and in 3 a large Gram-positive coccus in pairs and tetrads, apparently similar to Geirsvold's coccus. In 2 of these cases, growth was obtained from one specimen only, subsequent punctures were negative; in the third case, there was growth from a second specimen but not from 2 later ones. Wollstein looked upon this coccus as a contamination.

**Positive Results.** While many of the early writers reported the

presence of cocci or other organisms either in blood or spinal fluid obtained during life or in post-mortem material, it was usually without comment as to the possible etiological significance of the organisms found. Schultze (1898, S 21), however, at first believed that the specific agent of acute poliomyelitis was identical with that of cerebrospinal meningitis, of neuritis, and of encephalitis. But later (1905, S 22) he found diplococci in 2 cases that were not poliomyelitis (1 proved to be tuberculous meningitis) and suggested that caution must be used in interpreting the relation between the cocci and poliomyelitis; again in 1910 (S 23) Schultze definitely retracted his earlier view of the Weichselbaum diplococcus as the etiological agent of acute poliomyelitis.

Interest in cocci was also stimulated by Geirsvold's (G 6) observations during the epidemic in Norway in 1905. This author was able to cultivate a diplococcus or a tetracoccus from the spinal fluid in 11 cases of acute poliomyelitis and 1 case of acute polio-encephalitis. Harbitz and Scheel (1907, H 10), whose work covered the same outbreak, believed that the epidemic appearance of poliomyelitis pointed to an infectious disease caused by a living agent and referred in this connection to Geirsvold's coccus as though they believed in a possible relationship.

### Bacteriological Studies during the "Experimental Period"

**Negative Results.** The production of experimental poliomyelitis in monkeys and the evidence that the specific agent belongs to the group of ultramicroscopic viruses brought about a great change in the character of the bacteriological experimental work. Many of the investigators of this time had, however, already discarded any belief in a bacterial origin of the disease.

Römer, who carried on studies relative to the etiological agent over a period of years, both before and after the successful transmission of the disease to monkeys, sums up his work on bacteria in his monograph (R 25). He first made cultures from the pharynx and tonsils. The results disclosed the ordinary organisms. In the first experiments, the pneumococcus was found in excess of normal, in later cases, the *Staphylococcus albus*. But smears from the spinal fluid were always negative. Although many culture media were used and cultures made from spinal fluid, brain, pons and spinal cord, the tubes were sterile except in a few instances where growth was always identified as a common contamination. Examination of the blood in a severe case was also negative. No bacteria were found in stained sections. Therefore, Römer (R 21) says, he "was able to state with confidence that it was



impossible that a microbe which could be stained and cultivated easily could be the active agent in the causation of epidemic infantile paralysis."

Still other authors, whose names are associated with the early successful experimental work, described negative bacteriological results. Landsteiner and Popper (1909, L 11) in giving the source of the material for their first successful injection, cord emulsion from a fatal case, mention the fact that smears and cultures from the spinal fluid and central nervous system, and cultures from the spinal cord emulsion on agar, blood agar, serum agar, blood and serum bouillon, gave negative results. Leiner and von Wiesner (1909, L 28, I) felt that any growth obtained should be attributed to contamination and found that, in the case of spinal fluids, one source of error might be due to the fact that the first portion of spinal fluid obtained by lumbar puncture often contained an organism whereas later portions were negative.

In their third note, Flexner and Lewis (1909, F 41), while giving evidence that the specific agent is a filterable virus, state that no bacteria were discovered "either in film preparations or in culture that could account for the disease." In a "long series of propagations of the virus in monkeys, not one animal showed, in the lesions, the cocci described by some previous investigators" and no such bacteria were obtained from the human material examined. It was felt, therefore, that "they could be excluded from consideration." Flexner and Lewis had made a "painstaking study of film preparations and sections prepared from two specimens of human spinal cord and many specimens of the spinal cord and brain (and other viscera) obtained from monkeys, prepared and stained in the most various ways, but without finding either bacterial or protozoal parasites that could account for the infection."

Similarly, Wickman (1911, W 21) stated his conclusion as follows: "The results of experimental investigation have shown that the bacteria found have absolutely nothing to do with Heine-Medin's disease, and that in those cases in which they arose not from faulty technique, such bacteria must be regarded as having had an accidental and not a causal relation to the malady." And again, in his discussion of the experimental disease, Wickman says: "I, myself, notwithstanding the extensive material employed, could obtain only negative results with streptococcal injections. The time has fully arrived when such experimental investigations should be discarded from the literature of this disease."

Indeed, interest in the experimental disease and the nature of the virus so dominated the situation that but few references to a bacterial origin of the disease appeared between 1910 and 1916. Strauss and Huntoon (1910, S 64) isolated a coccus from one specimen of spinal fluid but not from another taken from the same case. They concluded that the bacteria reported in spinal fluids were either contaminations or secondary invaders. Robertson and Chesley (1910, R 20) came to a similar conclusion. Sections obtained from 6 cases and stained for microorganisms were uniformly negative. Spinal fluids from 20 cases were examined by the Minnesota State Board of Health. Geirsvold's diplococcus was found in pure culture in 7, and also in culture from blood, mouth, lung, spleen, kidney, middle ear, and brain substance of 1 case. Animal inoculation with these pure cultures produced some motor disturbances but the spinal cords did not show the specific lesions of poliomyelitis. This was regarded as the crucial test and confirmed the authors' opinion that Geirsvold's diplococcus was not the causative factor in poliomyelitis. The subject might have been considered closed but in 1916 and 1917 reports appeared almost simultaneously from several groups of workers describing the isolation of a coccus with claims for specificity.

### The Streptococcus—Etiological Significance

#### *Argument for Streptococci*

When Mathers published his preliminary report in 1916 (M 23) he was inclined to regard the micrococcus, isolated from the brain and cord of cases of poliomyelitis as a secondary invader. Further studies (1917, M 24) led him to believe that it was an important factor in the disease. In 9 out of 10 cases of poliomyelitis a peculiar polymorphic streptococcus-like organism was obtained from the tissues of the central nervous system in pure or mixed culture. In 5 cases the organism was isolated in pure culture from spinal fluid obtained after death. In 1 of 2 cases, this micrococcus was isolated from the mesenteric lymph nodes and kidneys. Cultures of the Berkefeld filtrates of brain tissue from 7 cases of poliomyelitis showed the organism in 3 instances. Cultures injected intravenously into rabbits produced paralysis of various groups of muscles and central nervous system lesions which were considered characteristic (hyperemia and edema of the tissues, with hemorrhages, round-cell perivascular infiltration, and neurophagocytosis in the cord). The coccus was demonstrated in the lesions both culturally and micro-



scopically. Anaerobic cultures of this coccus in an ascites-fluid medium corresponded to those of the virus both in the effect on the medium and in the morphology as shown in stained smears, where the organism appeared as minute Gram-positive coccus-like bodies arranged in pairs, groups and chains.

Working with Tunnicliff (M 27) and with Howell (M 26) Mathers demonstrated specific agglutinins, opsonins and complement-fixing bodies in the blood of rabbits which had been injected with various strains of poliomyelitis cocci. Mathers and Weaver (M 28; M 29) found that 2 strains of poliomyelitis cocci as well as hemolytic streptococcus, *Streptococcus viridans* and 1 strain of pneumococcus when grown on blood agar slants resisted the action of 50 per cent glycerol for 3 months. In 2 instances, poliomyelitis cocci in glycerinated spinal cord tissues were found viable after 15 months.

In addition, Mathers, Hektoen and Jackson (M 25) obtained fixed poliomyelitis material, mostly pieces of spinal cord, from various sources. These sections came from Boston, Minneapolis, New York City, Washington, D. C., and even from the 1906 epidemic in Norway. The time of autopsy was 1 to 78 hours after death. In 4 cases, no changes indicative of poliomyelitis were found. In these instances no bacteria were demonstrated. Definite coccal forms were found rather easily in all other sections. These cocci corresponded to those previously isolated in cultures of the central nervous system. This group of workers concluded, therefore, that micrococci occur with great regularity in the central nervous system in epidemic poliomyelitis and are not due to accident or contamination.

Nuzum and Herzog (1916, N 40) also isolated an organism, believed by them to be identical with that reported by Mathers (1916, M 23). In fact, the brains and cords obtained at autopsy were, in a number of cases, divided between Mathers and these authors. This Gram-positive micrococcus was obtained by culture of brain and cord in 13 out of 15 cases studied (Nuzum, N 36); in several instances from crypts of tonsils and from tonsils and mesenteric lymph nodes obtained at necropsy (M 23; N 40); from the spinal fluid obtained during life in 45 out of 50 cases (N 35). Control cultures of spinal fluids obtained from normal individuals or from patients suffering from other diseases were always sterile. Cultural and morphological characteristics corresponded to those described by Mathers. Inoculation of rabbits by various routes was followed by a paralysis which resembled poliomyelitis clinically but which differed histologically from the human disease in

that no perivascular infiltration was present and the infiltrating cells were probably not lymphocytes.

An immune serum with protective properties for white mice, rabbits and monkeys was prepared by injecting these micrococci into sheep and rabbits (N 35a). In addition, Nuzum and Willy (N 41; N 42; N 38; N 37; N 39) reported the production of a highly potent immune serum in the horse by repeated intravenous injections of aerobic cultures of the poliomyelitic coccus. This serum, they claimed, contained agglutinins, complement-fixing bodies and especially opsonins in high titer, and, when given early in the human disease, was effective in the prevention of paralysis. They also described experiments to show that this anti-poliomyelitis horse serum possessed protective and curative properties against the virus in the experimental disease in monkeys and that it neutralized the virus *in vitro*. The results obtained according to these authors pointed to an etiological relationship of the coccus to the disease.

Rosenow, however, has been the most zealous of the advocates of an etiological relationship between streptococci and epidemic poliomyelitis. Although he wrote in 1926 (R 44) that "only one question on poliomyelitis may be regarded as settled: the causative agent is a filter-passing virus," a long series of articles has been published to demonstrate Rosenow's conception of the relation between the virus and the peculiar pleomorphic, green-producing streptococcus announced in 1916 (Rosenow, Towne and Wheeler, R 53). This organism was first isolated from the throat, from material expressed from tonsils, and from abscesses in tonsils of a large series of cases of epidemic poliomyelitis. It was obtained from ventricular fluid after death, from blood during life in one instance (though there is no report of this having been confirmed later), from brain and cord, from intervertebral ganglia and from lymph nodes. Great variations in size and shape were noted according to the method of cultivation employed (R 53; R 52; R 54). On aerobic culture, the organism is irregular in size, resembling the ordinary green-producing streptococcus or pneumococcus of low virulence. On anaerobic culture, however, it grows very small, becomes filterable, and appears identical with the "globoid bodies" of Flexner and Noguchi. These variations are not due to contaminated or mixed culture according to Rosenow for all gradations are found both in cultures and in the tissues and the conditions favorable for the formation of one from the other, have been determined. Large forms have been observed in the tissues, breaking down into small ones. The coccus is resistant to glycerin for it was recovered in 4 cases from recently glycerinated pieces



of brain and cord (R 53) and has been "demonstrated in films and sections of brain and cord many months after they were placed in 50 per cent glycerol" (R 54). Moreover, "viability and specificity may be preserved for a long time by making dense suspensions in 50 per cent glycerol or preferably in two parts glycerol and one part saturated sodium chloride solution in water" (R 51).

In human cases, the streptococcus has been found to be present in adenoids and tonsils, in central nervous system lesions, in mesenteric lymph nodes, in spleen and liver (R 54; R 44). It has been isolated in pure culture from filtrates of nasopharyngeal washings and demonstrated in the nasopharyngeal swabbings of patients with poliomyelitis, contacts, and normal persons in the epidemic zone during epidemics, though absent in patients after recovery and in normal persons during non-epidemic periods (R 44). More recently, this organism has been demonstrated in stained smears of the spinal fluid in 23 human cases (R 46; R 47) and also isolated for the first time in pure culture from the spinal fluid during life in 5 cases and after death in 2 cases.

Although most of Rosenow's experimental work has been with rabbits, the coccus has also been isolated from the brain and cord of monkeys after intracerebral injection with fresh emulsion of brain and cord of human poliomyelitis, with glycerinated human virus, with glycerinated monkey virus (R 53) and with filtered virus (R 54). It was found in stained smears of the spinal fluid from each of 12 monkeys with typical poliomyelitis following intracerebral inoculation of virus (R 46; R 47); and cultured from the spinal fluid of each of 3 monkeys following inoculation of brain and cord from 3 fatal human cases, and from 1 of 9 monkeys with poliomyelitis following injection of the adapted virus (R 47). Streptococci were demonstrated in stained sections of the central nervous system of 54 out of 60 monkeys with typical symptoms and lesions following virus inoculation. Gram-positive cocci and diplococci were found in and adjacent to the lesions. Thirty-one of the 54 were anesthetized and 23 died from paralysis. No diplococci were found in 60 controls, 32 of which were anesthetized and 28 died from other causes (R 48).

In Rosenow's first report (R 53) there was described what was termed the "elective localizing power of the pleomorphic streptococcus." Intravenous or intracerebral injections of emulsions or cultures of the organism produced paralysis with central nervous system lesions in guinea pigs, rabbits, dogs, cats, and monkeys. The coccus could be recovered in pure culture from the nervous tissue and demonstrated microscopically in and adjacent to the lesions in the brain and cord.

Injection of aerobic cultures into monkeys (R 54), however, produced flaccid paralysis with characteristic though not typical changes in the cord but the classic picture as obtained with virus in this species was not secured. Rosenow suggested that this was due to the development of antibodies as the organism in the aerobic form has marked antigenic powers. Rabbits and guinea pigs were found to be highly susceptible to the streptococcus, but with the virus the conditions were reversed (R 44). In one instance a disease that "simulated" poliomyelitis was produced in a monkey with a filtrate of cultures (R 45).

Moreover, the serum of horses immunized with aerobic cultures of the pleomorphic streptococcus from cases of poliomyelitis in both man and monkey developed antibodies, agglutinins and complement deviating properties specific for the streptococcus. Rosenow found that the serum of patients and monkeys after an attack of poliomyelitis cross-agglutinated specifically many but not all of these strains in the lower dilutions (R 36). By agglutination experiments it was possible, moreover, to differentiate the pleomorphic streptococcus from the green-producing streptococcus occasionally isolated from the central nervous system of inoculated or uninoculated animals; the latter may be regarded as ante-mortem or post-mortem invaders. Rosenow and Gray (1918, R 50a) felt that these results support the view that the elective localizing power of the pleomorphic streptococcus as first demonstrated by Rosenow, Towne and Wheeler has significance and that it in some way bears etiological relationship to epidemic poliomyelitis.

In order to prove the presence of the organism of poliomyelitis (pleomorphic streptococcus) in the throat, Rosenow devised the precipitin reaction (R 41; R 44; R 43). This reaction was obtained by layering the cleared extract of nasopharyngeal washings from the suspected case on the anti-streptococcus horse serum. A positive reaction was reported in 83 per cent of cases of poliomyelitis and in 77 per cent of normal contacts. A relatively high per cent of positives was obtained with all persons within the epidemic zone and a low per cent in control groups outside of this zone. In patients with poliomyelitis, the reaction was usually positive during the epidemic and negative later.

Moreover, a skin test to determine susceptibility was reported (R 42; R 44; R 50). The antigen was obtained from freshly isolated strains of the pleomorphic streptococcus grown in pancreatic digest heart muscle broth with added ascitic fluid. The results of the skin test in 379 persons, 41 of whom had recovered from typical poliomyelitis, were interpreted as showing that the reaction was fairly specific. There



were no marked reactions in those that had recovered from poliomyelitis. In normal persons the incidence of positive reactions varied inversely according to age, corresponding in general to the age incidence of poliomyelitis. In 4 cases tested, the reaction was strongly positive during the acute stage, but became negative during convalescence. In tests on animals, the skin of most rabbits was found susceptible but the skin of monkeys (*M. rhesus*, Java, and baboon) was unsusceptible; this agrees with Rosenow's observations with regard to the susceptibility of these animals to inoculation with the streptococci.

Intravenous injections of the anti-streptococcus horse serum were reported to be of therapeutic value in the treatment of human poliomyelitis (R 37; R 39; R 54; R 38; R 40; R 51; R 47). Moreover, this serum has been thought by Rosenow to have neutralizing, protective and curative power against the virus of poliomyelitis in the experimental disease (R 36; R 54; R 47). Monkeys inoculated with an intracerebral injection of virus were treated with immune horse serum, intramuscularly, intravenously, or intraperitoneally, never intraspinally. Treatment was begun in some instances on the days of the intracerebral injections of virus, but usually after 1, 2 or 3 days had elapsed and, in a few instances, it was claimed, paralysis and death were prevented when serum was first given after the onset of symptoms. This treatment was considered successful because the average incubation period was longer (9.2 instead of 7.8 days), the incidence of paralysis was slightly less (84 instead of 90 per cent) and the mortality rate was much lower (38 instead of 75 per cent) in the 55 monkeys treated with immune horse serum than in the 20 controls treated with normal horse serum.

Similarly, the neutralizing effect of immune serum on the virus *in vitro* was shown by the lengthening of the incubation period, the lower incidence of paralysis and mortality as against controls with normal horse serum; the results were approximately as good as when human or monkey convalescent serum was used.

Prophylactic vaccination with the pleomorphic streptococcus was also attempted (R 47). Various antigens, such as living and heat-killed cultures, filtrates of cultures, and emulsions and filtrates of the brains and cords of rabbits and monkeys that succumbed after inoculation with streptococci, and various methods of injection were used. No method was found that invariably protected against the drastic method of intracerebral inoculation with virulent virus. But in 50 monkeys, immunized before receiving virus, the average incubation period was longer, and the incidence of paralysis and the mortality rate

was lower than in 23 unvaccinated controls. When immunization was obtained, it was usually so marked that the animal resisted repeated (as many as 7) intracerebral injections of virulent virus. Immunity was found to have developed as early as 15 days after the last injection of the immunizing antigen and persisted as long as 1 year after immunization. Serum from some of the immune animals neutralized virus *in vitro*.

In spite of all the evidence that is now available against the probability of an etiologic relation between the streptococcus and poliomyelitis, a new advocate has appeared in favor of the streptococcus as such an agent (Cooper, 1931, C 24). Green-producing streptococci were isolated from the spinal fluids of 65 per cent of the cases of poliomyelitis studied (total number not stated). Since the experimental work described brings out no new facts and since it was, moreover, all carried out with rabbits, it seems unnecessary to give the details here (see *Argument against Streptococci*).

#### *Argument against Streptococci*

It will be seen from preceding accounts that there are some workers who, while not denying that poliomyelitis is caused by a filterable virus, believe that this virus is only one stage in the life cycle of the agent, which appears in another stage as a pleomorphic streptococcus. No such cycle has yet been demonstrated with certainty for any of the other viruses and a very considerable amount of work has been done which in our minds is sufficient to disprove any etiological relationship between the streptococcus and poliomyelitis.

**Cultural and Morphological Tests.** Reference has already been made to the fact that many of the early workers were unable to demonstrate microorganisms in material from cases of poliomyelitis (human or experimental) either in smear or in culture; or, if such were found, they were easily identified as contaminants. Similar negative findings were obtained in studies made during the 1916 epidemic in New York. The largest series was that reported by Abramson (1917, A 2). Cultures were made from 1200 spinal fluids, withdrawn during all stages of the disease; except for evident contaminations all were sterile. Blanton (1917, B 15), Williams (1917, W 23), Norris, Shatara and Dean (1917, N 33), and more recently, Dath-Millet and Guempel (1931, D 4) in Belgium have also been unable in smaller series of bacteriological examinations of human spinal fluid or of autopsy material to demon-



strate an organism of apparent etiological significance. These negative results do not invalidate occasional positive findings.

Moreover, Olitsky, Rhoads and Long (1929, O 3) were unable to demonstrate streptococci in the spinal fluids of monkeys with the experimental disease. Streptococci were not found either in stained film preparations of centrifuged spinal fluids or in cultures of the fluids, even when Rosenow's yeast medium was used. These authors also emphasize the fact that this yeast medium contains streptococci, a fact brought out by Dr. Rosenow himself in his communication to them relative to the method of preparing the selective medium. Dr. Rosenow, however, stated that differentiation could be made "by the increased cloudiness of the inoculated tube as compared with the control tube of the inoculated extract of the same batch . . . and by differences in morphology and staining reaction. The streptococci that occur in the yeast extract are smaller, more slender, more uniform in size, less Gram-positive, and the margin is less distinct than the streptococci which we feel represent a primary growth."

In addition, Olitsky and his associates found that the cultural characteristics of a streptococcus isolated by Rosenow from human poliomyelitis spinal fluid corresponded closely with those of a streptococcus from the brain of a normal monkey, and with a streptococcus from the air of the laboratory.

Although many investigators have obtained only negative results (with, perhaps, an occasional contaminating organism) in their attempts to isolate cocci from poliomyelitic material, others have demonstrated micrococci with considerable regularity in such material. They were also able, however, to isolate similar organisms from other sources and thus concluded that there could be no special etiological relationship.

Tsen (1918, T 19) isolated streptococci from the central nervous system of monkeys that died during the course of experimental poliomyelitis and also from monkeys that died from other causes, as well as from the brains of normal rabbits. No difference could be detected in the characteristics of streptococci so obtained. Tsen concluded that these organisms invaded the tissues under conditions of lowered resistance.

Long, Olitsky and Stewart (1928, L 67) carried out a series of cultivation tests using the brains of monkeys with the experimental disease. In most instances, the animals were etherized soon after onset of paralysis; in a few cases, tissues were procured after the animal died. From each brain, cultures were made both from fragments and from emulsions

on a variety of media. In addition to the usual routine laboratory precautions, controls were cultured in a special room under aseptic precautions. It was found that a variety of ordinary bacteria, including non-hemolytic streptococci could be recovered from poliomyelitic monkey brains; they appeared irregularly in different portions of the same brain and more frequently in emulsions than in fragments; frequently they were found in cultures made in one room but not in another and more often with routine than with extraordinary precautions. These authors concluded that there was "evidently a correlation between the number of positive cultures with the number of bacteria in the air" and that "the notion that the bacteria were agonal invaders was not tenable" since the brains were removed while the animals were still strong.

Long and his associates then compared the cultural characteristics of 31 strains of non-hemolytic streptococci, poliomyelitic (including 7 strains from Rosenow) and non-poliomyelitic (a variety of sources). On rabbit's blood agar, most were green-producing. All grew profusely in fluid media. Long chained forms predominated. All showed pleomorphism.

Using Smith-Noguchi medium, these authors were also able to recover globoid bodies in 2 out of 14 monkeys. These bodies were definitely anaerobic, were distinct microorganisms and differed from the streptococcus of Rosenow. Inoculation of Rosenow's streptococcus into Smith-Noguchi medium and grown anaerobically failed to bring about their conversion to globoid form.

Heist, Solis-Cohen and Kolmer (1917, H 20) too had been unable to find anything resembling a transition between streptococci and globoid bodies. And Smillie (1918, S 47), in his report of cultivation experiments with globoid bodies made the statement that "nothing in this study has served to implicate the streptococcus in the pathology of the poliomyelitic process." Smillie did, however, find streptococci as common contaminants or secondary invaders, especially in animals that were killed when moribund or that had died sometime previous to autopsy.

The relation of coccal organisms to experimental poliomyelitis has since been investigated by Fairbrother (1929, F 2). Four groups of animals were studied: monkeys etherized during the initial stages of the disease, during late stages, after death, and normal monkeys or those with totally different diseases. Cocci were isolated, though irregularly, from the brain and blood of animals in each of these groups.



Moreover, similar coccal organisms were obtained from the air of the room in which the work was conducted. The general cultural and morphological characteristics of the cocci from these different sources were similar and were also present in certain cultures examined of the genus *Micrococcus* as well as in cultures made by Rosenow from poliomyelitic material. Minor differences observed might have been expected from the pleomorphism claimed for this coccus. Fairbrother concluded from his study that these cocci "have no etiological relationship to the disease," and that they are "members of the group of air micrococci and occur as air-borne contaminants, although under certain circumstances they may be found as terminal invaders, arising probably from the naso-pharynx."

**Filterable Phase of Streptococci.** The important questions as to whether streptococci, as well as other bacteria, may pass through a filterable phase and especially whether in this invisible stage, they are identical with the ultramicroscopic viruses have recently been the occasion of considerable study. In particular, concrete experimental evidence has been brought forward to show that the Rosenow streptococcus may be filtered through Berkefeld N candles but that this filterable form is not identical with the virus of poliomyelitis (Richardson and Mellon, 1932, R 15). Intracerebral inoculation of 2 strains of this streptococcus into rabbits produced a cerebral meningitis; the original organism was recovered from brain cultures but not from heart blood cultures. Brain emulsions from these animals reinoculated into other rabbits, again resulted in recovery of the streptococcus. Intracerebral inoculation of rabbits with Berkefeld N filtrates of these emulsions was without effect. Intensive cultivation of the brain emulsion filtrates by the Hauduroy transplant method on blood agar plates resulted in the recovery of an organism resembling microscopically and culturally the streptococcus of the original strains.

Cultures of the 4 strains were then injected intraperitoneally into rabbits and the peritoneal exudate obtained was added to sterile broth. These lysates were filtered through Berkefeld N candles and the filtrates cultivated as before. A streptococcus resembling the Rosenow strains was finally obtained. Agglutination tests were not carried out; the authors felt that the important point was not whether the streptococcus recovered from the filtrates was identical with the original Rosenow streptococcus, as filtrates do not always yield at once the identical organism, but whether this filterable form was identical with the poliomyelitis virus.

Berkefeld N filtrates had been made of 24 hour broth cultures of the two Rosenow strains as first received. No growth was obtained by plate-to-plate cultivation. The filtrates were then divided into two portions and sealed in ampoules. One set was incubated at room temperature and one at 37°C. About 5 months later, sediment or opalescence was observed in the filtrates kept at 37°C. and plating resulted in the recovery of a streptococcus believed by the authors to be identical with the original strains. They therefore felt "justified in concluding that these two strains of streptococci recovered by Rosenow from cases of anterior poliomyelitis are, at certain phases of their growth, filterable through Berkefeld N candles."

However, monkeys injected intracerebrally with filtrates from the 2 cultures, did not develop poliomyelitis within a month's observation period (this part of the experimental work was carried out by Dr. C. W. Jungeblut). This fact seemed to the authors "rather definite evidence that these filterable forms are not identical with the virus of poliomyelitis."

**Resistance of Cocci to Glycerin.** Mathers and Weaver (1918, M 29) obtained micrococci in culture from nervous tissue of cases of poliomyelitis that had been preserved 15 months in 50 per cent glycerin; but other streptococci and pneumococci were also resistant. Long and Olitsky were able to cultivate streptococci (1929, L 64) from pieces of brain tissue that had been kept in 50 per cent glycerol for 303 days, but not after 333 days. Fairbrother (1929, F 2) compared the effect of glycerin on the micrococci isolated in the investigation referred to above with that on 14 other cocci isolated from poliomyelitic and non-poliomyelitic tissues and from the air. Those from the first group were found to have survived the action of 50 per cent glycerin for 70 days and those from the second group for at least 16 days. Fairbrother concluded that resistance to glycerin was not a property that would distinguish cocci from poliomyelitic material from those obtained from other sources.

The virus of poliomyelitis, however, has been shown by Rhoads (1929, R 7) to be active after preservation in glycerol for 8 years. No streptococci, however, were found in cultures of the glycerolated material made before inoculation.

**Effect of Concentration.** Poliomyelitis virus concentrated *in vacuo* proved more effective than either the original brain cord suspension or the filtrate therefrom and the virus retained its potency in the concentrate for more than 4 months, even in a solution saturated with NaCl



(Clark, Shindler and Roberts, 1930, C 16). But streptococci from poliomyelitis cases, similarly concentrated in a filtrate of normal brain cord suspension, did not survive more than 35 days. This circumstance, Clark and his associates felt, would "tend to discredit the streptococcus as the specific etiologic agent." These authors also made many attempts "to cultivate a significant organism from the highly infective concentrates and dialysates but with negative results. Streptococci were found as a contaminant in one instance only." Stained smears showed "nothing that could not be found in the 'dialysate' from normal sources."

**Effect of the Streptococcus on Cerebrospinal Fluid Sugar.** If the streptococcus, found by some workers in the spinal fluid of cases with poliomyelitis, ferments dextrose, the sugar content of the fluid should be low, thus resembling the finding in streptococcus meningitis. Fremont-Smith and Daily (1931, F 63) determined the spinal fluid sugar in 71 cases of acute poliomyelitis. The values varied from 51 to 97 mgm. per 100 cc.; in 90 per cent they lay between 51 and 75 mgm. Thus the sugar content was considered normal, confirming the work of A. G. Kelley (K 6), who had found this spinal fluid sugar content in 3 cases of poliomyelitis to be 0.060 per cent.

### **Immunity Tests with Streptococci**

**Serological Reactions.** In 1916, Kolmer and Freese (K 20) carried out a series of complement-fixation tests between salt solution suspensions of streptococci, diplococci, diphtheroids and Gram-negative bacilli cultured during life from the spinal fluid of patients with poliomyelitis or from various tissues after death, and the spinal fluids or sera of patients during or after an attack or of normal controls. With large doses of antigens, a small percentage, 6 to 9 per cent, of weakly positive reactions was obtained with the spinal fluids of 35 persons and the antigens of the diplococci and streptococci. All tests with sera were negative with all antigens. The authors concluded that these microorganisms may possess sufficient virulence to produce antibodies but that this did not necessarily indicate that they were to be regarded as the cause of the disease.

The cultures of non-hemolytic streptococci studied by Long, Olitsky and Stewart (L 67) showed a marked heterogenicity in direct and cross-agglutination tests and also in precipitin tests. Pooled serum from monkeys, recovered from poliomyelitis and from normal monkeys as

controls, failed to agglutinate any of the 31 strains including the 7 from Rosenow.

Fairbrother (F 2) also performed agglutination tests with serum from patients recently recovered from poliomyelitis and from others of long standing and the cocci isolated in the study described above. These sera contained neutralizing substances for the virus as proved by monkey experiments but the results of agglutination were practically negative.

**Neutralization Tests.** Rosenow's anti-poliomyelitic serum and the serum of Nuzum and Willy were tested for their protective power by Amoss and Eberson in 1918 (A 21; A 22). Monkeys receiving these sera intraspinally and virus intravenously developed experimental poliomyelitis whereas immune monkey serum protected against the disease. In fact, these 2 anti-poliomyelitic sera seemed to act in the manner of normal horse serum to promote rather than to prevent infection. It was also shown that Nuzum and Willy's serum did not neutralize the virus *in vitro* and did not possess curative properties against an intracerebral inoculation of virus, although given intravenously, intraspinally and intramuscularly.

Thus, the antibodies present in the blood of monkeys recovered from the disease would seem to be distinct from those developed in the horse by treatment with streptococci.

Amoss and Eberson conclude that if "the antibodies yielded by the streptococci differ essentially from those induced by the virus of poliomyelitis, the contention that virus and streptococci are identical becomes untenable."

Rosenow's anti-poliomyelitic serum both concentrated and unconcentrated failed to neutralize the virus *in vitro* in tests made by Stewart and Haselbauer (1928, S 56). Morgan and Fairbrother (1930, M 46) also obtained negative results in neutralization tests with a commercial sample of Rosenow's concentrated anti-poliomyelitic serum.

**Attempted Production of Poliomyelitis in Animals by Inoculation with Streptococci.** The supporters of the streptococcus as an agent of etiological significance in poliomyelitis have reported that the inoculation of this organism into animals, especially into rabbits, produced a disease identical, both in clinical and pathological findings with poliomyelitis as observed in man or in monkeys inoculated with the filterable virus.

Reference is made in another section to the experimental work of the earlier investigators. Streptococci of various origins were injected into



animals, most often rabbits, with resultant nervous symptoms, paralysis, and sometimes central nervous system lesions but in no instance was a disease produced that resembled epidemic poliomyelitis. Although not recognized at the time that some of this early work was carried out, it is now well known that rabbits are often affected by spontaneous encephalitis and that the pathology of this disease may simulate that of other central nervous system affections. As Rivers has said (Discussion of Cooper, C 24) "the rabbit is a notoriously poor animal for the study of experimentally induced lesions in the nervous system, because it is subject to at least two diseases, virus III infections and infections with Microsporidia, which may spontaneously attack the brain and cord" (see *Section on Rabbits and Other Laboratory Animals*).

An extensive investigation of the pathologic effects of streptococci was reported by Bull in 1917 (B 40). Of 78 rabbits inoculated intravenously with streptococci from cases of poliomyelitis, 4 developed flaccid paralysis of the extremities, 14 meningitis, and 30 infections outside the central nervous system, most often arthritis, but also tenosynovitis, myositis, endocarditis, etc.

The histological findings were carefully compared with those typical of the human disease and of the experimental disease in monkeys following injection of virus. The lesions in rabbits showed a meningitis, usually purulent, focal or general. There were focal abscesses in the gray matter; areas of necrosis of nerve cells with infiltration of lymphocytes, and some perivascular infiltration. Stained preparations showed many streptococci, with frequent phagocytosis; focal abscesses contained streptococci in masses, suggesting embolic origin. Examination of stock rabbits revealed infections that suggested that the perivascular lesions may have existed in the animals prior to the injection of the streptococci. Moreover, rabbits injected with streptococci derived from conditions other than poliomyelitis showed symptoms and lesions indistinguishable from those produced by streptococci of poliomyelitic origin. The conclusion was that if large numbers of sufficiently virulent streptococci are injected into rabbits intravenously, they localize in the meninges and may invade the cerebrum; next to the meninges, the joints may be affected, then the muscles, and finally other organs. But it was evident that the central nervous system lesions in rabbits injected with streptococci could not be identified with those of poliomyelitis in man or monkeys.

Bull was also unable to produce paralysis or any condition resembling poliomyelitis in monkeys by the intravenous injection of streptococci

obtained from poliomyelitic sources either directly or after passage through rabbits. Bull regarded the streptococci isolated from the brain or cord of monkeys dying after inoculation with the virus as secondary bacterial invaders.

Somewhat similar results were reported by Kolmer, Brown and Freese (1917, K 21). Intracranial, intravenous and intraperitoneal injection of the organisms cultivated from the spinal fluid and the tissues of cases of poliomyelitis failed to produce paralysis in rabbits or monkeys. Arthritis and meningitis were produced by streptococci but there was neither clinical nor histological evidence of true poliomyelitis.

The fact that the filterable virus of poliomyelitis survives only 4 days in the brain of the rabbit was brought forward by Amoss (A 13) as additional evidence of the fact that the virus differs fundamentally from the streptococcus and that the latter cannot be considered the cause of epidemic poliomyelitis.

Pleomorphic streptococci, culturally and morphologically similar to those isolated from cases of poliomyelitis, were found by Sherwood and Downs (1919, S 39) to have a wide distribution; they were demonstrated in the throats of 20 to 25 per cent of normal persons, not associated with any outbreak of the disease. These organisms were classed by the authors as *S. salivaricus* and proved to be pathogenic for young rabbits; when injected intracerebrally, they remained localized in the nervous system; when injected intravenously, they appeared in the central nervous system within 3 or 4 hours. Inoculation was followed by a rise in temperature, loss of muscle tone, and occasionally flaccid paralysis with permanent impairment of the legs. Central nervous system lesions were observed: hyperemia, frequent hemorrhages, increase in round and neuroglia cells, and perivascular infiltration of round cells.

Bull's work was confirmed in detail by Long, Olitsky and Stewart (1928, L 67). Intracerebral injection of cultures of streptococci (from poliomyelitic or non-poliomyelitic sources) produced in rabbits a purulent meningo-encephalitis, often complicated by a streptococcic septicemia. No signs or lesions typical of poliomyelitis were observed.

That the Rosenow spinal-fluid strain of streptococcus acted in a similar manner was later reported by Olitsky, Rhoads and Long (1929, O 3). The microscopic findings corresponded with those previously noted.

Fairbrother too has been unable to find lesions entirely analogous to those of poliomyelitis in rabbits injected intravenously with the cocci



isolated from various sources. In the animals that died soon after injection, a purulent meningo-encephalitis was found; in those that showed few symptoms some round-celled perivascular infiltration was seen. But "no evidence was obtained to support the etiological relationship of the coccus to this disease from rabbit experiments."

**Cultivation of the Virus—"Globoid Bodies."** In 1910, Flexner and Lewis (F 42) noted that turbidity developed when bacteria-free filtrate of virus was mixed with rabbit's serum or human ascites bouillon and incubated, but they were unable to prove that this turbidity was caused by a living organism.

In 1913, Flexner and Noguchi (F 48; F 49) described minute formed structures, which they referred to as globoid bodies, cultivated by special methods from nervous tissue of human or experimental origin or from filtrates. A liquid culture medium of human ascitic fluid with a fragment of sterile rabbit's kidney proved most suitable for the initial growth, which was visible at first only as a gradually diffusing opalescence; later, particles formed and fell to the bottom. In a semi-solid medium (2 per cent agar added to the above), minute colonies formed, consisting of globoid bodies, 0.15 to 0.3 micron in diameter, in pairs, chains, and small masses. Cultivation was conducted under anaerobic conditions. Initial growth could be obtained by replacing either rabbit kidney or ascitic fluid by other corresponding substances though not in the absence of both. This indicated that growth was derived from the material inoculated and not from the medium.

The bodies stained more intensely with Gram's stain in older cultures than in the initial ones. After several weeks they became enlarged though still filterable through Berkefeld filters.

Although not all cultures produced infection, on inoculation into monkeys, others proved to be pathogenic even to the eighteenth or twentieth generation (representing a calculated dilution of the original virus of 1:24<sup>17</sup>).

The authors expressed the view that an etiological relationship existed between the cultivated microorganism and human or experimental poliomyelitis.

Further work with these strains was described in 1915 (Flexner, Noguchi and Amoss F 50) and, in 1917, Amoss (A 12) reported that 2 additional cultures of globoid bodies had been recovered from the central nervous system of monkeys with experimental poliomyelitis. These were identical with the original cultures of Flexner and Noguchi. As had been previously shown, the highly parasitic cultures were refractory

to artificial cultivation but after long cultivation *in vitro* they became saprophytic and grew more readily.

Tsen (1918, T 19) attempted to repeat the work of the above investigators. He was able to find "organisms similar to the globoid bodies culturally, morphologically and in staining reactions" but was not able to carry the culture for more than three generations. The cause of this failure was not apparent. Tsen brings out two points which he considered evidence against the supposition that the globoid bodies are the causative agents of poliomyelitis: "First, the globoid bodies have not yet been proved to be able to produce immunity against poliomyelitis, and, second, the serum of monkeys immunized with the globoid bodies has failed to show neutralizing power against poliomyelitic virus" (Amoss, A 12).

Subsequent statements by Amoss and by Flexner would suggest that they, too, no longer believed the globoid bodies to be the causal factor. In 1926, Amoss (A 17) said, "In fact the proof that globoid bodies constitute the etiological agent is as yet inadequate;" in 1928, Flexner (F 17) made the statement: "The virus of which I speak has not been certainly seen, has only a few times, if ever, been enriched by cultivation outside the body, and has not yielded unmistakably to study the many characteristic qualities which we so readily obtain and so insistently demand in studying the usual pathogenic or disease-producing bacteria."

Much the same conclusion was drawn by Krauspe (1928, K 35). In the course of cultivation experiments in which fresh organs in an ascites medium were used, he obtained growth similar to that described as characteristic of globoid bodies. Krauspe felt, however, very critical with regard to these experiments as he had not been able to produce poliomyelitis in monkeys by injection of the cultures.

The subject might, therefore, be considered closed, if it were not for the fact that two recent reports have again brought up the question. Long, Olitsky and Rhoads (1930, L 66) attempted to repeat the earlier work on the subject and, in particular, to test the pathogenic power of the cultures. Fragments of brain and cord or Berkefeld N filtrates of nervous tissue from 7 monkeys, successfully inoculated with poliomyelitis virus, were used to inoculate 315 culture tubes (fluid medium). Minute objects, resembling globoid bodies were found in 36. Subplants did not convince the authors of the presence of any living microorganism.

"Nevertheless, when washed sediments from subplants of one of the strains, representing the seventh, eighth, ninth, and tenth transfers,



were inoculated into monkeys, the clinical signs and pathological effects characteristic of experimental poliomyelitis could be induced. The virulence of the 'cultures' could not be ascribed to carrying over the original material into these remote subplants since the seventh transfer represented a dilution of the original cultivated material to about  $1.5 \times 10^{-12}$  and the tenth, to about  $1.3 \times 10^{-18}$  if one assume, as the transfer technique justifies, a thorough mixing of the contents of each tube. On the contrary, it appears as if the poliomyelitic virus had multiplied *in vitro* and had increased as a consequence of being in a medium of a modified living tissue-cell culture. . . .

"There remains for consideration the problem of the selective pathogenicity of the 'cultures'; only the material of those tubes of the ninth and tenth transfers, which showed the 'globoid bodies' proved pathogenic; those respective tubes of the same transfer which were free from the minute bodies but apparently identical in all other respects, were avirulent. It may be that the virus was adsorbed to the particular bodies which we have found in the 'cultures' and which resemble closely the globoid bodies of Flexner and Noguchi. Further elaboration of this study would be necessary, however, before such an inference could be regarded as a definite hypothesis."

A claim for the cultivation of an organism from filtrates of the poliomyelitic virus has also been put forward by Eberson (1932, E 1, E 2). A brain tissue medium was used. The organism was described as a minute ovoid body, occurring in irregular clusters, in pairs, singly, or in short chains. No statement was made as to the possible relationship of these organisms with the globoid bodies previously described. Experimental poliomyelitis was produced in monkeys by the inoculation of cultures in the sixth to the thirteenth subplants. Further reports confirming this work will be awaited with interest.

In the meantime, we may close the section on the cultivation of the virus with a statement from Dr. Rivers (personal communication to Dr. Park), "I do not believe that globoid bodies represent the etiological agent of poliomyelitis."

## THE VIRUS

### Preliminary Experiments

**Early Experimental Work.** In the earliest experimental work on animals, bacterial cultures obtained from a variety of sources—seldom from cases of poliomyelitis—were injected in an attempt to reproduce the lesions of this disease. Rabbits were most frequently employed.

In many of the animals so inoculated, nervous symptoms, sometimes paralyses, developed. Usually no bacteria were found in the cord but there were, perhaps, small myelitic foci with alterations most marked in the gray matter, more or less alteration in the ganglion cells, and some vessel changes. Hoche (1899, H 28) combined some other material as starch or lycopodium granules with the cultures; arterial injection then produced local inflammatory cord changes of parenchymatous nature.

Although others had used sterilized streptococcus cultures, Roger (1892, R 31) was one of the first to work with the living organism. He produced a progressive muscular atrophy in rabbits following inoculation with a weakened culture of streptococcus. Autopsy revealed chiefly alterations of the ganglion cells of the anterior horns.

Others to use cultures of streptococci were Bourges (*Strep. erysip.*, 1893, B 24) and Vidal and Besançon (streptococci of various origins, 1895, V 3), who like Roger were unable to find bacteria in the cord; and B. Morel and Rispal (1895, 1896, M 45), who recovered streptococci in the blood vessels, anterior horns, and central canal of the cord after intravenous injection.

Although the results of these and other similar experiments were negative as far as the production of a true poliomyelitis was concerned, they gave a certain support to the view that many affections of the cord, both those of the degenerative and those of the inflammatory type are of an infectious nature.

Wickman (1905, W 20) closes his discussion of the work of the early investigators with the statement: "There is, I believe, no doubt that no one of the authors mentioned has been able to produce the picture of a disease with associated alterations that presents even a vague resemblance to poliomyelitis acuta."

Wickman's own experiments in this field were carried out with a streptococcus culture originally obtained from Homén. This strain had shown neurotropic properties which Wickman attempted to increase by repeated passage through the nervous system of a rabbit. After the ninety-third passage, 15 rabbits were injected intravenously with a bouillon culture. Although some muscular weaknesses developed, in no case was a true paralysis observed, nor were any poliomyelitic changes demonstrable microscopically. Wickman's closing paragraph is significant: "Definite conclusions can be drawn from the experiments only when, in the first place, the specific micro-organism is known and, in the second place, when we have an experimental animal that reacts to it in the same way as man does."



Bülow-Hansen and Harbitz (1899, B 38) seem to have been the first to attempt to reproduce the disease by using material obtained from a human case of poliomyelitis. They inoculated a rabbit with a cord emulsion subcutaneously with negative results. Spinal fluid from the same case was injected into a rabbit intraspinally and into 2 mice subcutaneously, also with negative results. Later, Guinon and Rist (1903, G 20), inoculated 2 rabbits intravenously with 1 cc. of spinal fluid from acute cases. Their results were negative.

### Transmission of Poliomyelitis to Monkeys.

**Landsteiner's Original Experiment.** Wickman's second requirement concerning a suitable experimental animal was fulfilled a few years later. At a medical meeting in Vienna, December 18, 1908, Landsteiner and Popper (L 10) demonstrated microscopical preparations from 1 human and 2 monkey cords. The human section showed the marked pathological changes of acute poliomyelitis. The material was obtained from a boy of 9 years that had died after an illness of 3 days. Cultures of the cord were negative as were the results of injections of the material into rabbits, guinea pigs, and mice. An emulsion of the cord was also injected into 2 monkeys intraperitoneally. One, a *Cynoceph. hamadryas*, died 8 days after the injection, after an illness of 2 days; no paralysis was noted but this could have escaped observation. Histological findings showed a typical high-grade poliomyelitis, agreeing with the human picture. Similar changes but of less intensity were found in the cord of a second monkey, a small *M. rhesus*. In this animal, a complete flaccid paralysis of the posterior extremities was observed after 17 days, though the condition otherwise was good; this monkey was killed 2 days later. Two other monkeys, injected with the cord of the *M. rhesus*, showed no evidence of illness at the time of writing, 10 days later. A more complete account of this experiment was published on May 25, 1909 (L 11). At this time, the authors made the suggestion that the disease might be caused by a so-called invisible virus.

Landsteiner's results were soon confirmed by Knoepfelmacher (October 31, 1909, K 18). Intraperitoneal inoculation of a *M. rhesus* with a suspension of cord from an acute case produced typical poliomyelitis. The attempt to transfer the disease to a second generation was unsuccessful.

**Transmission in Series.** Success in serial transmission, however, was announced soon after by several groups of authors in quick succession: Flexner and Lewis (November 13, 1909, F 39), Leiner and von Wiesner

(November 18, 1909, L 27), Landsteiner and Levaditi (November 27, 1909, L 5), Römer (December 7, 1909, R 21), Landsteiner and Prasek (December 11, 1909, L 12).

Flexner's first report (F 39) gives an account of the transmission of the disease to the third generation, thus proving its infectious nature. The lumbar cord was obtained 26 hours after death from a patient dying on the fifth or sixth day after the appearance of the paralysis, and a portion, emulsified in salt solution, was inoculated intracerebrally into monkeys (variety not stated), about 12 hours later. An emulsion of the spinal cord of the monkeys that developed paralysis was used for passage inoculation. The cerebral cortex also proved active. These were the first experiments with the M.A. virus that has since been used so extensively by Flexner and others.

Very little was added to the knowledge of the experimental disease by the brief note of Leiner and von Wiesner's (L 27) success in the transmission of poliomyelitis, also to the third generation of monkeys, but Landsteiner and Levaditi's report (L 5) brought out two important points. In order to transport the material (dorsal and lumbar cord from an acute case) from Vienna to Paris, it was preserved for 4 days in 33 $\frac{1}{3}$  per cent glycerin before being inoculated intraperitoneally into a chimpanzee. Passages of the cord of this animal by intracerebral and intraperitoneal inoculation into 2 *M. cynomolgus* resulted in paralysis on the fifth day with typical lesions. A first attempt at filtration of the cerebral emulsion through a Berkefeld V candle gave a positive result, thus giving confirmation to Landsteiner and Popper's supposition that the virus belongs in the category of filterable microorganisms. Additional proof was brought forward by Flexner and Lewis in their third note, December 18, 1909 (F 41). The cord of a monkey with the experimental disease proved virulent for another monkey on intracerebral inoculation after having been preserved in glycerin (concentration not stated) for 7 days. The cord of this animal was also active, again demonstrating as shown in the above experiments that the effect was produced by a living virus and not by an adherent toxic body. Moreover, the filtrate of a cord emulsion after being passed through a Berkefeld filter (grade not stated), was infective so that these authors also concluded that "the infecting agent of epidemic poliomyelitis belongs to the class of the minute and filterable viruses that have not thus far been demonstrated with certainty under the microscope."

These important early experiments thus proved, without a doubt, that the etiological agent of epidemic poliomyelitis was a living virus



and that the monkey was a suitable experimental animal in which both the clinical picture and the pathological findings of the human disease could be reproduced. A vast amount of work has since been carried out in an effort to define the properties of the virus, the routes by which inoculation can take place, the distribution of the virus within the body, the probable path of entry and mode of elimination, immunity principles, etc.

### Properties of the Virus

**Filterability: Size.** Reference has been made above to the fact that both Landsteiner and Levaditi (L 5) and Flexner and Lewis (F 41) found the filtrate passed through a Berkefeld filter active. The possibility of this activity being due to soluble toxic bodies and not to a living organism was excluded by these same workers (Flexner and Lewis, January 1, 1910, F 42; Levaditi and Landsteiner, January 3, 1910, L 44) when they showed that the disease could be transmitted in series, using the spinal cord of a monkey that had been inoculated with a filtrate sterile for ordinary bacteria. Landsteiner and Levaditi also showed that the virus passed through Chamberland filters (L 5), through Reichel filters A and B, and through Berkefeld N candles (L 44). Leiner and von Wiesner (L 28, II) obtained positive results after passage through Bukall filters although they were unsuccessful with Reichel filters.

Some workers (Leiner and von Wiesner, L 28, II; Zappert, Z 2; Levaditi and Landsteiner, L 44) have noted a prolonged incubation period, thus indicating to them a weakened virus when filtrates were used. That this may have been due to adsorption of particles containing the virus is suggested by the work of Clifton and his associates in their ultrafiltration studies. These authors found that the concentration of the virus in the first portion of the filtrate was materially decreased by adsorption, thus making it necessary to discard the first 10 to 20 cc.

During the past few years, efforts have been made to determine more nearly the size of the virus. It has been shown that it passes easily through a Berkefeld V candle, less easily through an N candle, and is diminished in quantity by passage through a W candle; it also passes through similar grades of Chamberland filters (Amoss, 1928, A 18).

Amoss (A 18) also states that, using 100 pounds pressure, the virus if given time would pass through a layer of congealed gelatin of 5 mm. thickness, and that the virus cannot be differentially centrifuged by the method used for vaccine virus.

More exact studies on the size of the virus have been attempted by Krueger and Schultz (1929, K 36) and by Clifton, Schultz and Gebhardt (1931, C 17). The earlier report stated that the lower limits had not been fixed but that the results indicated that the magnitude of the virus was less than  $300\mu\mu$ . In the later study, the authors described the preparation of acetic-collodion membranes for ultrafiltration purposes. The lipoids and some of the protein in the virus suspensions were first removed by ether extraction to reduce adsorption. In later experiments large protein aggregates were further removed by protein precipitants such as basic lead acetate. The results "indicate that the magnitude of the virus of poliomyelitis lies below  $50\mu\mu$  in diameter." In subsequent work (personal communication to Dr. Park) the results of several experiments suggested a magnitude below  $25\mu\mu$ . "Vaccinia virus (Levaditi) and herpes virus (Goodpasture) in the form of virus brain suspension, under comparable conditions proved no more filterable than the virus of poliomyelitis" (Schultz, Gebhardt and Bullock, 1931, S 17).

**Preservation in Glycerin.** As already mentioned, Landsteiner and Levaditi's first experiment (1909, L 5) on the transmission of the disease to monkeys in series was carried out with nervous tissue that had been preserved 4 days in  $33\frac{1}{3}$  per cent glycerin, and Flexner and Lewis (1909, F 41) soon after found that the activity of comminuted spinal cord was not destroyed by suspension in glycerin (concentration not stated) for 7 days. It was already known that bacteria were less resistant to the action of glycerin than were the viruses of vaccinia and rabies, so these facts gave ground to the belief that the active agent of poliomyelitis belonged to the class of ultra-visible viruses. Rosenow, however, has stated that the pleomorphic streptococcus of poliomyelitis can be preserved many months in glycerin (see *Section on Bacteriology*); Long and Olitsky (1929, L 64) found streptococci viable in pieces of brain tissue, preserved in 50 per cent glycerol for 303 days, but not after 333 days; while Mathers and Weaver (1917, M 28, M 29), as was previously mentioned, recovered the "poliomyelitis cocci" in glycerinated spinal cord tissues after a period of 15 months. The virus of poliomyelitis has been shown by various workers to survive glycerination as follows: 142 days in pure glycerin without diminution of potency (Römer and Joseph, R 30); virulence decreased on preservation "for a long period" in 50 per cent glycerin (Lentz and Huntemüller, 1910, L 30); virus K retained its activity undiminished after 25 months in 50 per cent glycerin at  $4^{\circ}\text{C}$ . (Flexner, Clark, and Amoss, 1914, F 36); virus kept



6 years in glycerol but the virulence had declined (Flexner and Amoss, 1917, F 25). The longest period of survival has been reported, however, by Rhoads (1929, R 7). A mixture of the M. A. and K viruses had been kept for 8 years in 50 per cent glycerol at 4°C. The first intracerebral inoculation with the glycerolated tissue proved successful, thus showing that the original high infectivity of these strains had been preserved for this long period. Cultures made before inoculation showed that streptococci were absent.

**Resistance to Drying.** Early work showed that the virus was active after various methods of drying. According to Flexner and Lewis (1910, F 42), virulent cord was still active after being dried over caustic potash for 7 days; Levaditi and Landsteiner (1910, L 44) found an emulsion active when dried *in vacuo*, over sulphuric acid for 15 days; virus completely dried and preserved in the presence of phosphorus pentoxide maintained its virulence for at least 24 days (Landsteiner, Levaditi and Pastia, 1911, L 8). Römer and Joseph (1910, R 26) dried spinal cord 28 days *in vacuo* and found it still virulent.

Leiner and von Wiesner (1910, L 28, II and IV), however, obtained a contrary result. Inoculation of a spinal cord emulsion dried at 37° in the incubator for 4 hours or at room temperature for 24 hours was inactive (no control experiment recorded). Leiner and von Wiesner felt that their results differed from Flexner's because the emulsion, after removal of the coarser particles, was dried in thin layers. This would correspond more closely to the natural method.

**Resistance to Freezing.** The virus resists freezing for short periods of time but not indefinitely. It has been found to be active after having been frozen for 4 hours (Leiner and von Wiesner, 1910, L 28, II); for 11 days (Landsteiner and Levaditi, 1909, L 5); for 40 days at -2° to -4°C. in the Frigo apparatus (Flexner and Lewis, 1910, F 42); but not active after 1½ to 3 years (Flexner, Clark, and Amoss, 1914, F 36); it was also active after 50 days at a temperature of about +4°C. although autolysis had softened the cord and mold covered the specimen (Flexner and Lewis, 1910, F 42).

### Effect of Heat

**Body Temperature.** As the virus survives and probably multiplies in the human body at 37°C., it might be assumed that this temperature would not render it inactive under experimental conditions. This is in accord with early observations. Leiner and von Wiesner (L 28, II),

to be sure, reported inactivation after heating the virus for two hours at 35°C. but Landsteiner and Levaditi (L 5) found a Berkefeld filtrate active after 7 days at 38°C.; Flexner and Lewis (F 47) found virus effective after 20 days and Levaditi (L 32; L 33) after 21 days at 37°C.

**Temperatures above 37°C.** With regard to higher temperatures, however, the reports on the degree of heat necessary to cause inactivation seem conflicting, although Amoss (1928, A 18) states quite definitely that the thermal death point is 50°C. for 30 minutes, and Shaughnessy, Harmon and Gordon (1930, S 31) conclude from a review of the literature that it probably is between 45° and 50° for 30 minutes, as tested by intracerebral inoculation into monkeys. The lack of uniformity in the results may be due to several reasons: the virus used has not always been of the same potency; in some cases filtrates of different types and in others emulsions have been used, so that the coarseness of the particles may have affected the penetration of the heat; the dosage has varied; both the subcutaneous and intracerebral routes of inoculation have been tried; the time interval as well as the degree of temperature has been varied.

Using an emulsion, Römer and Joseph (1910, R 27) found the virus attenuated but still virulent on intracerebral inoculation after heating 30 minutes at 45°. Kling and Pettersson (1914, K 15) found it virulent in 0.75 cc. amounts for intracerebral inoculation after 30 minutes at temperatures from 40° to 47.5°C.; and Abramson (1918, A 5) reported virus effective on subcutaneous inoculation after being heated for the same period at 50°C. Howitt (1930, H 33) failed to destroy the virus by treating with certain chemicals and heating to 55° and 58°C. though temperatures of from 71° to 78°C. did destroy it.

On the other hand, Flexner and Lewis (1910, F 47), reported that filtrates were ineffective when heated 30 minutes at 45° to 50°C. Leiner and von Wiesner (1910, L 28, II) inactivated cord emulsion by heating it for 60 minutes at 50°C. or for from 15 to 20 minutes at 60°C.; Römer and Joseph (1910, R 27) rendered 5 per cent emulsions ineffective for subcutaneous inoculation in 30 minutes at 45° to 55°C., and for intracerebral inoculation at 50° to 55°C.; and Kling and Pettersson (1914, K 15) obtained negative results with the intracerebral inoculation of 0.75 cc. of crude virus heated 30 minutes to 47.5° or 50°C.

Shaughnessy, Harmon and Gordon (1930, S 31) have recently described a series of experiments in which the factors of time, temperature, potency of virus, and amount of inoculation were varied. Berkefeld V filtrates of 5 per cent emulsions of spinal cord and brain in normal



saline were used (Aycock strain). They conclude that, in the absence of a method for standardizing the potency of the poliomyelitis virus, the exact thermal inactivation point cannot be determined. If the amount inoculated was small (2 cc.) and the potency moderate, the inactivation point was low, about 42.5°C. for 30 minutes. But a temperature of 55°C. was effective for all periods from 5 to 30 minutes. The minimum temperature, when large doses (4 cc. intracerebrally and 10 cc. intraperitoneally) of a moderately virulent virus were used, was 52.5°C. for 30 minutes. Lower temperatures (such as 42.5°C.) seemed to bring about attenuation of the virus or else destroyed a part of it so that small doses were ineffective in producing the disease.

**Effect of Light.** The virus is readily destroyed by sunlight (Flexner, 1916, F 15a); and is killed by light in the presence of eosin (Amoss, A 18).

**Effect of X-ray.** The effect of X-ray on the virus of poliomyelitis *in vivo* is discussed in a later section (*Treatment in the Experimental Disease*). Lenz and Jungeblut (1932, L 31) have also tested its effect *in vitro*. A 10 per cent cord suspension was exposed to large doses of X-ray, (200 KV, 8 MA, 2 cm. wood filter, 50 cm. target distance, 38 minutes). Three monkeys were then inoculated intracerebrally with 1 cc. of the treated emulsion; all developed poliomyelitis after incubation periods of 6, 12, and 13 days, respectively. Although the incubation period was slightly prolonged in 2 instances, the authors concluded that, under the conditions employed, exposure to X-ray failed to destroy, or even markedly to attenuate the virus.

### Effect of Chemicals

**Disinfectants.** Of the disinfectants tested, bichlorid of mercury, formaldehyde, and certain oxidizing agents have been found to be effective, while phenol in the percentages used did not destroy the virus.

*Bichlorid of Mercury.* The statement has been made (Amoss, 1928, A 18) that weak solutions of mercury bichlorid destroy the virus.

*Formaldehyde.* Destruction of the virus by exposure of dried spinal cord for 7½ hours to the action of formalin vapor as used in ordinary room disinfection was described by Römer and Joseph (1910, R 26, R 25). While Abramson and Gerber (1918, A 6) found that the virus in a 10 per cent brain cord emulsion was not destroyed by contact with 0.5 per cent formaldehyde for 4 hours, treatment of the centrifuged supernatant of an emulsion with 0.4 per cent formalin for 5 days at

room temperature has proven effective (Jungeblut, personal communication).

*Oxidizing Agents.* The virus appears to be readily destroyed by oxidizing agents.

*Action of Chlorin in Water.* The effect of chlorin on the virus of poliomyelitis added to water has recently been studied by Levaditi, Kling and Lépine (1931, L 43). They showed that 4 mgm. of chlorin per liter in 24 hours sterilized cloudy water, that contained much organic matter, and was rich in virus; 0.4 mgm. per liter sterilized virulent limpid water. Thus, chlorination of drinking water with these quantities of chlorin would suffice to protect against the possible transmission of the virus by water.

*Hydrogen Peroxid.* A 1:5 dilution of Merck's perhydrol in saline mixed with equal parts of virus emulsion destroyed the virus after 45 minutes contact at 37°C. (Levaditi and Landsteiner, 1910, L 48). Flexner and Lewis (F 45) found that the virus was "quickly" destroyed by a 1 per cent solution of hydrogen peroxid.

*Potassium Permanganate.* A 2 per cent solution of potassium permanganate with equal parts of virulent emulsion destroyed the virus after an hour's contact at 37°C. (Levaditi and Landsteiner, 1910, L 48).

*Phenol.* Phenol (0.5 per cent) did not destroy the virus in human spinal cord preserved in the refrigerator for 15 months. Moreover, a Berkefeld filtrate, containing almost no coagulable protein, and treated with 0.5 per cent phenol was infectious after 20 hours and 5 days at 22°C. (Flexner, Clark, and Amoss, 1914, F 36). Kraus (1911, 1931, K 27, K 29) also tested the effect of phenol on filtered virus (paper filtrates). He found that even after preservation for a month in the ice chest, 1 per cent phenolized virus was capable of producing infection if injected intraperitoneally or intracerebrally, but not if injected subcutaneously.

*Antiseptics.* A few antiseptic solutions have been tested for their effect *in vitro*.

*Menthol.* Two cubic centimeters of a virulent virus emulsion treated with 0.5 cc. of a 1 per cent solution of menthol oil for 2 hours at room temperature produced only transient symptoms in a monkey (intracerebral inoculation of 0.5 cc.). A similar result was obtained when the virus emulsion was treated with a powder composed of menthol, salol and boric acid (Levaditi and Landsteiner, 1910, L 47).

*Thymol.* Thymol in solution (thymol 2 grams, water 1000,



alcohol q. s. to dissolve the thymol) did not destroy the virus *in vitro* (equal parts of thymol solution and virulent cord emulsion) (Levaditi and Landsteiner, 1910, L 48).

*Hexylresorcinol.* Hexylresorcinol solution has shown no virucidal effect *in vitro* (Jungeblut, 1930, J 16).

*Ether.* The virus is not affected by ether (Amoss, 1928, A 18). But the virus apparently is not taken up by ether extraction. Howitt (1930, H 33) was unsuccessful in extracting a potent virus from an acetone precipitate with alcohol and ether; and Clifton, Schultz, and Gebhardt (1931, C 17) found that inoculation of the layer of ether solution after extraction of the lipoids in the virus suspensions produced poliomyelitis in monkeys only exceptionally.

*Miscellaneous.* Howitt (1930, H 33) treated a Berkefeld V filtrate of a 10 per cent virus suspension with a number of chemicals in order to show whether the virus could be precipitated without loss of virulence and recovered again from the precipitate after removal of proteins and certain salts. Howitt, herself, draws no conclusion from the results which do not seem clear-cut. Under certain conditions, the virus was precipitated by 1 per cent aqueous safranin, and by acetone; one may also conclude that it was not destroyed by the addition of such substances as basic lead acetate, barium acetate, sodium bicarbonate, and acetic acid.

Although antimony compounds offered some promise of success in the treatment of the experimental disease, Jungeblut (1930, J 16) found that solutions of antimony were not virucidal *in vitro*.

The action of sodium citrate on the virus is important because of the possible effect when testing citrated serum or plasma for neutralizing power. Rhoads (1931, R 10) concluded that sodium citrate in a concentration of 1.5 per cent exerts an "inhibitory chemical effect on the filtered virus."

*Chemotherapy.* The prophylactic or curative effect of antiseptic solutions and drugs is described in a later section (*Treatment of the Experimental Disease*).

**Conservation of the Virus in Water, Milk, or Butter.** The possible transmission of the virus by water or by food is discussed in the *Chapter on Epidemiology*. The following tests have a bearing on this question.

**Conservation in Water.** Landsteiner, Levaditi, and Pastia (1911, L 8) found that virus mixed with sterile water and kept at room

temperature out of light for 25 days was active for monkeys. The incubation period was prolonged, however, indicating to the authors an attenuated virus. More recently, Kling, Levaditi, and Lépine (1929, K 13) showed that cord emulsion, diluted with a fairly large quantity of sterile faucet water, was virulent after preservation for 114 days at room temperature out of light.

**Conservation in Milk.** Landsteiner, Levaditi, and Pastia (L 8) carried out an experiment with milk, similar to the one described above for water. The virus proved to be potent after preservation in sterile milk for 31 days at ordinary room temperature out of light. Bristol and Thomson report that the virus was still alive, in milk kept at about 10°C., at the end of 150 days (personal communication to Dr. Park).

**Conservation in Butter.** Butter has also been tested for its effect on the pathogenicity of the virus (Kling, Levaditi, and Lépine, 1931, K 14). Virus mixed with butter (both commercial butter and butter made by the authors by adding 5 per cent lactic acid to the cream) and kept at a low temperature ( $-2^{\circ}\text{C}.$ ) retained its virulence for monkeys for 2, 11, 20, and even 91 days.

**Action of Bile.** A paper filtrate of the virus was unaffected by the action of normal monkey bile *in vitro* (4 hours at room temperature and 10 hours in the ice box) (Landsteiner, Levaditi, and Pastia, 1911, L 8). Leiner and von Wiesner (1911, Z 3) had also carried out *in vitro* experiments. They found that normal bile (human or monkey) did not destroy the virus; but that, in the 2 instances tried, bile from animals that had recovered from poliomyelitis protected when mixed with virus *in vitro* (see *Section on Distribution of Neutralizing Substances in the Body*). Leiner and von Wiesner felt that no conclusion could be drawn from 2 cases but that the possibility of microbicidal antibodies in the biliary secretion of monkeys with the experimental disease must be considered. More recently, Levaditi, Kling, and Lépine (1931, L 43) have stated that normal bile exerted no antiseptic action in a period of 24 hours.

**Action of Gastric and Intestinal Secretions.** The virus can survive the action of gastric and intestinal secretions for at least two hours (Flexner, Clark, and Dochez, 1912, F 37) (see also *Section on Intestinal Secretions under Distribution of the Virus in the Body*).

**Action of Nervous Tissue.** Landsteiner, Levaditi, and Pastia (1911, L 8) were unable to show that nervous substance, either from a normal, or from an infected monkey, exerted any neutralizing effect *in vitro*.



Similarly, Leiner and von Wiesner (1911, Z 3) found that the only effect of the addition of rabbit brain or of fresh lecithin (10:100) to active virus was to retard the appearance of paralysis 4 or 5 days.

The work of Landsteiner, Levaditi, and Pastia has been confirmed recently in experiments carried out by Jungeblut (1932, J 20). The virulence of virus filtrates was found to be practically unaffected by the addition of normal monkey cord or brain, or of inactivated poliomyelitis cord. Thus it would appear that the virus cannot be fixed or absorbed by nervous tissue *in vitro* (see also *Effect of Dilution*). In 1 out of 3 instances, however, Jungeblut found that convalescent cord, removed the second month after infection and therefore presumably free from virus (see *Section on Persistence of the Virus in the Body*) was capable of inactivating a virus filtrate.

**Effect of Dilution and of Certain Tissue Constituents.** As this subject has recently been discussed by Jungeblut (1932, J 20), the following is taken from his article:

"The appearance of inhibiting substances in bacterial cultures which have passed the acme of growth, has been repeatedly described for a large number of microorganisms. In the virus field, Sittenfield, Johnson and Jobling (S 46) have recently reported on the presence of a growth-inhibitory factor in the tumor tissue of the Rous chicken sarcoma, an observation which was immediately paralleled by a similar finding of Murphy and his co-workers (M 56). The first reference to an analogous phenomenon with the poliomyelitis virus may be found in an early statement of Leiner and von Wiesner (L 28, III) *i.e.*, that virus cord suspensions of higher concentrations tend to be less virulent than those containing the virus in more dilute form. In view of the general biological significance of the problem, we have undertaken to repeat more systematically the work of the latter investigators.

"Three groups of monkeys, comprising four animals each, were inoculated intracerebrally with 1 cc. of graded virus cord suspensions. The concentration of the centrifuged suspensions varied from as high as 40 per cent to as low as 0.1 per cent in the different groups. The results of the three tests [show] that between definite limits of concentration, the titrations progress in an orderly manner, the virulence of the virus diminishing at the same rate as the concentration of the tissue emulsion decreases. In contrast with this, certain more concentrated suspensions, although containing theoretically multiple quantities of virus, invariably cause a much lighter infection. These conclusions are based on the length of the incubation period and the extent of paralysis in the respective animals.

“Our observations thus far seem to be in perfect harmony with the statement of Leiner and v. Wiesner, which we quoted before. However, while there is ordinarily a particular virus concentration with maximum virulence, above and below which the dilutions become progressively less virulent, it is not possible to predict with accuracy which suspension in a series of given dilutions will ultimately prove to be the most virulent one.”

In the next experiment an attempt was made to determine whether there was an inhibitory factor in the tissue emulsion which could be removed by filtration. In 3 out of 5 tests, it was found that Berkefeld N filtrates were somewhat more virulent than the virus suspension. Admitting that there is an inevitable loss of virus through adsorption to the filter candle, Jungeblut finds “that the traditional belief that filtrates of poliomyelitis virus are generally less virulent than suspensions, is open to serious criticism.”

An attempt was then made to restore the “hypothetical inhibitory factor” by adding various tissue constituents to the virus filtrates *in vitro*. The results obtained with normal monkey nerve tissue, with inactivated poliomyelitic nerve tissue, and with convalescent cord have been given in the preceding section. In contrast to the inability of nervous substance to fix or adsorb the virus were the results with mixtures of virus filtrates and normal monkey testicle. In 3 out of 4 instances these mixtures had lost the greater part of their virulence; the loss of virulence was more conspicuous in the supernatant fluid than in the sediment. Normal rabbit testicle, on the other hand, has been thought to enhance the action of virus filtrates *in vitro* (Thompson, 1930, T 8).

**Optimum Hydrogen Ion Concentration.** According to unpublished experiments of Amoss and Aycock (cited by Amoss, 1928, A 18, p. 170), the virus remains viable at least 48 hours at hydrogen ion concentrations, varying from pH 5.0 to 8.2. In Howitt's experiments (H 33), it was not destroyed by acidification to pH 4.4.

**Electrical Charge of the Virus.** Observations on the behavior of other viruses in an electrical field have led to the study of the effect of cataphoresis on the virus of poliomyelitis. Olitsky, Rhoads, and Long (1929, O 2) and Ionesco-Mihaiesti, Tupa, Wisner and Mesrobianu (1929, I 3) have found that, under the usual conditions of hydrogen ion concentration (pH 6.9 to 8.0 is the range given by the Rumanian workers), “the virus of poliomyelitis as such, or associated with particles in fine suspension, migrates in an electrical field to the anode. It follows



that the virus bears an electro-negative charge." It corresponds in this respect to vaccine virus which also migrates to the anode.

**Adsorption, Elution, and Purification of the Virus.** By a process of adsorption and elution, it has been found possible to obtain the poliomyelitis virus in a dilute solution, freed, at least to a considerable extent, from the tissue substances which are closely associated with it. As Sabin's report (1931, S 1) covers the important facts in the literature in addition to giving his own results we may quote from his article, which describes "a method whereby the virus of poliomyelitis may be partially purified, and ultimately perhaps be obtained in its pure state. The method follows closely the procedures which enabled Willstätter and his co-workers to isolate enzymes in their purest known form. Numerous investigators (Levaditi and Nicolau, 1923, L 49; Lewis and Andervont, 1927, L 55) have reported the capacity of various suspensions to adsorb filterable viruses. The adsorbed viruses are in most instances inactivated, and in the case of poliomyelitis, Amoss (1928, A 18) states that 'the presence of colloidal substances with adsorptive power destroys the virulence after 1 or 2 days.' Rhoads (1931, R 12) described the adsorption and inactivation of poliomyelitis virus by aluminum hydroxide, type 'C' of the Willstätter series, and showed that adsorption occurred at pH 5.5 and 7.0, but not at pH 8.8. Gilde-meister and Herzberg (1924, G 8) succeeded in adsorbing bacteriophage on kieselguhr and subsequently eluting it with dilute ammonia. Kligler and Olitzki (1931, K 10) confirmed these observations on bacteriophage, and were able to do the same with fowl-pox virus, using kaolin as the adsorbing agent."

Sabin added virus filtrate to alumina gel "C," acidified with  $M/15$   $\text{KH}_2\text{PO}_4$ . The supernatant liquid was poured off and the sediment obtained was washed with distilled water and then mixed with  $M/15$   $\text{Na}_2\text{HPO}_4$ . An eluate was thus obtained that was colorless and water-clear. The original virus filtrate, the adsorbed supernatant liquid, and the eluate were then tested for the presence of virus by intracerebral inoculation into monkeys. The adsorption of the virus had apparently been complete as the monkeys injected with the adsorbed supernatant liquid showed no symptoms; the animal injected with the  $M/15$   $\text{Na}_2\text{HPO}_4$  eluate developed typical poliomyelitis in 5 days, and those injected with the original virus filtrate in 6 days. Quantitative tests indicated that 80 to 90 per cent of the organic constituents of the original virus filtrate were contained in the inactive adsorbed supernatant liquid.

**Concentration of the Virus.** In 1912, Flexner, Clark, and Fraser (unpublished work cited by Clark, Schindler, and Roberts, 1930, C 16) distilled filtrates *in vacuo* at temperatures of 20° to 30°C. without injury to the virus, while Kling and Pettersson (1914, K 15) concentrated 1 liter to 200 cc. in the Faust-Heim apparatus at 35° to 38°C. and found the concentrate virulent. Amoss and Taylor (1917, A 24), concentrated normal nasopharyngeal washings, to which active virus filtrate and sodium bicarbonate had been added, *in vacuo* at 37°C., from 50 to 2 cc. The resulting liquid after dialyzation through collodion was infective.

A more extensive investigation has been made of this subject by Clark, Schindler, and Roberts (1930, C 16). These workers found that the concentrated residue after distillation *in vacuo* was more potent than either the original brain cord suspension or the filtrate therefrom. The virus remained potent in a "concentrate" containing NaCl to saturation for more than 4 months. No important loss of potency was noted after dialyzation of the "concentrate" against sterile distilled water. The demonstration of the virus in the water-soluble portion of the dialysates and not in the water-insoluble or euglobulin fraction nor in the concentrated diffusate, together with the results of fractional precipitation by  $(\text{NH}_4)_2\text{SO}_4$  indicated that the virus remained constantly associated with the pseudo-globulin fraction of the proteins.

In a paper as yet unpublished, Clark and Ainsworthy (personal communication to Dr. Park) report success in concentrating the virus of poliomyelitis by adapting Seibert's (S 29) ultrafiltration method so that aseptic procedures could be used. Alundum cups were impregnated with 10 per cent gun cotton in glacial acetic acid and then washed and autoclaved. With these filters, an infective ultraresidue was obtained while the ultrafiltrate was never infective even when concentrated *in vacuo* and subsequently injected.

A different procedure has been employed by Sabin (S 2) in an attempt to concentrate purified virus (see preceding section). Dialysis through very dense collodion membranes was followed by distillation *in vacuo* at a temperature not exceeding 30°C. to about one-hundredth the original volume. A dose of 0.0005 cc. of virus, thus concentrated, produced typical paralysis in monkeys. After further purification by adsorption and elution, again followed by dialysis and distillation, a water-clear preparation was obtained which produced paralysis with 0.0003 cc. Less than 50 per cent of the virus was recovered in the concentrate after the above process had been carried out. One avenue of loss proved to be by diffusion through the very dense collodion bags which



were used, a fact of some significance with regard to the minute size of the virus aggregate (see *Section on Filterability and Size of the Virus*).

**Titration of the Virus.** Comparison of experimental results is often difficult because of the lack of a standard dosage. Of especial interest, therefore, is Brodie's work (1932, B 31) on the titration of the poliomyelitis virus in terms of lethal dosage. After carrying out a series of tests which showed that the monkeys employed had a fairly uniform susceptibility to the experimental disease, many specimens of virus were titrated. The minimal completely paralyzing dose was then defined as the "smallest quantity of virus containing tissue that will produce a complete and rapid paralysis in a monkey weighing 2.5 to 4 kilos within 13 days." In Brodie's experience "less than a M.C.P. dose either failed to produce symptoms or at most produced paralysis after a prolonged incubation period. More than a M.C.P. dose invariably produced severe paralysis."

It was found that similar areas of the central nervous system taken from different animals contain approximately the same infective dose.

**Survival of the Virus in a Refractory Host.** In the course of his investigation on the transmission of poliomyelitis to rabbits, Marks (1911, M 21) reported that monkeys inoculated with filtrates of nervous tissue of rabbits that had died following the intravenous or intraperitoneal injection of virus developed the disease. This would suggest that the virus was deposited in the nervous tissue of the rabbit even though typical lesions were not found, and that it was not destroyed in the interval before passage, that is, 8 to 15 days, or the incubation period in the rabbit as observed by Marks. Marks also cited a verbal communication from Flexner and Clark to the effect that the poliomyelitis virus survived "for a period of days" in the subcutaneous tissues of the rabbit.

It has sometimes been suggested that certain refractory animals, such as rats, might act as a reservoir for the virus. Levaditi and Danulesco (1912, L 37) tested, therefore, the duration of the survival of the virus in these animals. They were unable to recover virus from an emulsion of nervous tissue, spleen and mesenteric lymph nodes, 4 or 5 days after intraperitoneal inoculation. Guinea pigs were also inoculated intraperitoneally; virus proved to be present in the peritoneal fluid removed 20 to 24 hours later but could not be demonstrated in nervous tissue or in an emulsion of spleen, mesenteric lymph nodes, omentum, and liver in animals sacrificed 3 and 15 days after inoculation. But spinal ganglia placed in the anterior chamber of the eye of a rabbit preserved their virulence 3, 9, and 23 days.

Amoss (1918, A 13), on the other hand, showed that, while the poliomyelitis virus survived in the rabbit brain for 4 days, it could not be detected by reinoculation into the monkey at the end of 7 days. In the rat brain, the virus did not survive 4 days (Amoss and Haselbauer, 1918, A 23).

While attempting to adapt the poliomyelitis virus to the rabbit by testicular passage, Thompson (1930, T 8) found that the virus did not survive 24 hours in the rabbit testicle although this tissue not only did not destroy the virus *in vitro*, but apparently enhanced its action. A similar effect had been observed by Duran-Reynals (1929, D 32) for vaccinia virus.

Virus in collodion sacs placed in the peritoneal cavity of rabbits survived for 10 days although in monkeys, under similar conditions, it did not remain viable more than 48 hours (Jungeblut and Hazen, 1930, J 23).

**Effect of Vaccine Virus.** Early in the history of the experimental disease Thomsen (1911, 1912, T 10, T 11, T 9) reported experiments in which the poliomyelitis virus was mixed with smallpox vaccine and then applied cutaneously as in vaccination. The monkey died in 9 days with histological changes typical of poliomyelitis. Thomsen believed that the virus proliferated in the pustules. Material from the pustules, which developed on the above monkey, was emulsified and applied, by cutaneous vaccination to 2 other monkeys. Both developed poliomyelitis with typical pathological findings.

Thompson (1930, T 8), however, could find no evidence that vaccine virus mixed with poliomyelitis virus lengthened the period of survival of the latter in the rabbit testicle.

In view of the increased incidence of post-vaccinal encephalitis during the past few years, the work of Hurst and Fairbrother (1931, H 44) is significant. They infected a monkey simultaneously with poliomyelitis virus and a highly virulent vaccine virus (neuro-vaccine) and concluded that the latter had no power to modify the nervous lesions of poliomyelitis, whether injected directly into the brain or inoculated intradermally. Nor could they demonstrate any activating effect of vaccinia on a weak poliomyelitis virus.

**Production of Toxin.** It has been generally accepted that transmission of experimental poliomyelitis in series proved that the disease was due to a living virus and not to a toxin. This would not eliminate the possibility of a toxin, secreted by the specific agent as in the case of diphtheria and tetanus. No experimental proof of the existence of



such a toxin has been brought forward. However, Collier (1927, C 21) makes the statement that, since the virus is found only on mucous membranes and within the nervous system and since the virus is not conveyed by the blood stream, it follows that the swelling and degeneration found in lymphoid tissues and in the liver and spleen must be the result of a toxin produced by the virus.

The League of Nations Monthly Epidemiological Report (March, 1930, L 17) also advances the hypothesis that "the pathogenic agent, located in the region of the tonsils and pharynx, secretes a toxin which has a predilection for the central nervous system." After citing the work of various authors especially that of Fairbrother and Hurst (see *Chapter on Pathology*) relative to the spread of the virus along the axis-cylinders, and comparing these observations with the known facts in regard to the propagation of tetanus and diphtheria, the following conclusion is drawn: "The poliomyelitis virus appears to spread along the nerve fibers. The mode of propagation is thus rather that of a toxin and not that of a presumptive micro-organism. . . . The existence—which is not open to doubt—of a route of entry either through the pharynx or through the tonsils also points to the possibility that poliomyelitis is a localized disease involving the production of toxin." There is, however, no evidence of a toxin acting upon cells where the virus is not present. The virus is certainly not confined to the upper respiratory tract.

### Strains—Variations in Virulence

**Strains.** Although the human disease was successfully transmitted to monkeys almost 25 years ago and a vast amount of experimental work has since been carried out, one is struck by the fact that relatively few strains of the poliomyelitis virus have been isolated and carried through several monkey series in passage and thus made available for scientific study. The ease or difficulty of implanting a human strain in monkeys is probably determined by a combination of factors. Monkeys are not naturally susceptible to the disease and some monkeys are more resistant than others; the pathogenicity of the virus may vary; the quantity of the virus present in the original inoculated material may not always be the same, depending on the portions of the central nervous system used and on the stage of the disease during which it was secured; or "auto-sterilization" may have taken place.

It was early (Flexner and Clark, 1911, F 33; Flexner, 1912, F 13)

suggested that different strains or races of virus existed, if virulence could be considered a criterion. The 10 strains of human virus with which these authors had worked in America had all been successfully implanted in monkeys but only about one-half of the specimens of cord tested in Germany, Austria, and France had been successfully inoculated and an even smaller number could be transmitted in series. Levaditi, Gordon, and Danulesco (1911, L 41) obtained successful transmissions in 3 out of 4 instances with material sent to them from England; 14 years later, Levaditi wrote to Gordon (W 2) saying that one of these strains (derived from a subject, with ascending paralysis, that died on the fifth day of the disease) was by far the most powerful virus he had yet received. McIntosh and Turnbull (1913, M 4) were also able to transmit the disease in series with nervous tissue from 2 of 3 cases that died in the acute stage; the failure was with a specimen taken from a sporadic case, the successes were with nerve substance from cases that occurred during a mild epidemic; it was suggested that this fact might explain the difference in pathogenicity. The Swedish virus of 1911 has been mentioned (Flexner, F 13) as the most powerful one investigated up to that time (1912). This conclusion was based on the reported success in transmitting the disease with nasopharyngeal or intestinal washings. But, as has been pointed out elsewhere (*Section on Distribution of the Virus in the Body*), the criteria of the experimental disease upon which this report was based have not been generally accepted.

Even though the inoculation of the human material results in infection, the virus may become attenuated and die out in the course of a few passages, or even the first passage may fail. Several Rumanian investigators (Ionesco-Mihaiesti, Tupa, Wisner, Mesrobeanu, 1928-1929, I 2, I 4) have made a study of certain irregular strains of this type isolated during local epidemics in 1927 and 1928. In the first group of 10 cases studied, positive results were obtained with material from 6 only. It is perhaps important that these 6 patients died during the first 7 days of the disease while the other 4 died toward the end of the second week. Material from the latter number gave negative results in spite of repeated inoculations of the same monkey or of the use of new monkeys. In the second epidemic material from 3 cases was inoculated with 1 positive result; the duration of the illness of this patient had been 4 days; of 1 of the other 2, 18 days; the third died a few hours after admission to the hospital but the date of the onset of the illness is not given. No passage was accomplished with the 1 positive of this



set. In the first set, successive passages were marked by an increase in the incubation period, milder symptoms with subsequent recovery, and later a failure to transmit the disease.

It has elsewhere been noted (*Section on Persistence of the Virus in the Body*) that the virus has only exceptionally been recovered from the cord by inoculation tests after the thirty-third day and by cataphoresis only as late as the twenty-third day. Moreover the infectivity of the cord, in the experimental disease, has been found to diminish with regularity so that 8 days after the height of the paralysis, the strength of the cord virus was only one-eightieth of that originally present. It has been suggested by Brodie (B 31) that this might be due to one of two factors; the presence of neutralizing substances in the blood or the removal of the virus by phagocytic cells. This rapid decrease in infectivity may afford one explanation of the failure to induce the disease with the human material in the above instances and in other similar ones. Moreover, since the quantity of virus present in different portions of the nervous system varies, an emulsion may be rendered less effective by the inclusion of portions, such as brain substance, which ordinarily contain only small amounts of virus.

The Rumanian workers, however, looked upon their findings as confirmation of the conclusions of Levaditi, Sanchis-Bayarri and Schoen (1928, L 50) with regard to "neuro-infections mortelles auto-stérilisables." These authors advanced the theory that when the neurotropic ultra-viruses (of epidemic encephalitis, herpes, rabies) invade the central nervous system, they set up both a degenerative and a defensive process. The defensive process tends to destroy the virus *in situ*, a condition necessary to effect a cure; but the reaction may be so intense that it is incompatible with life, and death follows instead of recovery. Thus an animal may die as the result of a virus inoculation but the virus cannot be demonstrated in the nervous tissue by passage inoculation because the reaction has destroyed the virus as well as the animal. This explanation may not be inconsistent with Brodie's suggestion with regard to the removal of the virus by phagocytic cells (see *Chapter on Pathology*).

The proportion of successful inoculations with human strains may, however, be increased by the re-inoculation method as described under *Allergy* in the *Chapter on Resistance and Immunity*.

The reason for the failure to obtain infection with subsequent inoculations of the cord of an affected monkey when the first inoculation with human nervous tissue has been successful, is not known. It has

been supposed (Flexner, 1931, F 20) "that degeneration or virus metabolic products contained in the human cord act to make the originally inoculated monkey more susceptible to infection."

Moreover, "a degree of inconstancy is encountered even in dealing with the most highly potent virus strains for which adequate explanation is not at hand" (Rhoads, 1931, R 13). Sometimes a filtrate proves to be less active than usual although the animal from which it was obtained was sacrificed promptly at the onset of paralysis. Rhoads suggested that this might be due to the quantity of virus units in the nervous system of a particular monkey or that the process of extracting the virus might have an adverse effect.

As much of the experimental work reported in the literature is carried out with a few strains of known potency, brief mention may be made of some of them here and of the source from which they were obtained. The M.A. virus, often referred to as a "weak strain," was isolated in 1909 from the lumbar cord of a child dying on the fifth or sixth day after the appearance of a paralysis which affected the lower extremities (Flexner and Lewis, F 39). The K virus was also obtained from a human cord in 1909 (Flexner and Lewis, F 39, F 40); in this case death occurred on the fourth day, and lesions were extensive throughout the cord. This strain proved to be more potent than the preceding one. An "immunizing" strain was described by Flexner and Amoss in 1924 (F 30) and is discussed in the *Section on Active Immunization*. Another widely used strain, the Ay (Aycock strain) apparently gives varying results in the hands of different workers as it is termed "highly active" by some and "weak" by others. Warburg (W 4) refers also to the "weak" Mt.S. strain; a pooled virus from 3 human cases sent to Rockefeller Institute by Mount Sinai Hospital; and to the strong P.M.V. strain, a pooled monkey virus, a mixture of the M.A. and K strains.

The question of the biologic identity of strains isolated in different parts of the world as shown by cross-immunity or neutralization tests is discussed in the *Chapter on Resistance and Immunity*. Special mention may be made here, however, of the fact recently brought out by Weyer (1931, W 16) that continued passage of a virus through monkeys had apparently brought about some alteration in the virus; an antiserum obtained by injecting horses with this monkey virus effected neutralization in high dilutions but was relatively ineffective against freshly isolated human strains. It is interesting that Römer (R 25) mentioned the possibility that transference of the virus to monkeys caused some biologic change in the virus.



**Variations in Virulence.** The earlier reports on the effect of animal passage on the virulence of the virus were somewhat conflicting. Leiner and von Wiesner (1909, L 28, I) noted no increase or diminution in virulence in the first generations; Landsteiner and Prasek (1909, L 12) doubted that virulence was decreased by serial transmission; while Flexner and Lewis (1910, F 45) reported that the K virus (see preceding section) was now in the twenty-fifth generation and could be regarded as having attained a maximal potency, and again in 1911, Flexner and Clark (F 33) observed that human strains of the virus produced a less severe and less fatal disease experimentally until they became adapted to the monkey organism. Pettit (1925, P 15) later described a continuous increase in virulence by passage over a period of 7 years. In 1917, a given dose of virus was followed by death in 15 to 18 days; in 1921, the period had decreased to 7 days and in 1924, to 4 days.

Certain observations on fluctuation in virulence are especially important with regard to the epidemiological features of the disease. As noted above, by successive passages through monkeys, human strains may reach a high degree of virulence for this animal. Flexner, Clark, and Amoss (1914, F 35) described specific instances of this change. Whereas several cubic centimeters of the original emulsion had been necessary to produce infection, later 0.1 to 0.001 cc. of a Berkefeld filtrate was sufficient. Moreover, in the first generations, many monkeys failed to develop paralysis or recovered after paralysis, but, after adaptation of the virus, paralysis and death occurred in every case. The M.A. strain illustrated this description. It was carried through a long series of passages, from the fall of 1909 to the winter of 1912, and maintained the maximal activity, acquired early in the period, for about 3 years. Then its action became irregular and the infective power diminished gradually but not regularly, until it returned to the original level. Meanwhile, samples of cord and brain of all animals, dying from the experimental disease, were kept in 50 per cent glycerin at 4°C. In 1918, after having shown a low level of virulence for 6 years, a high degree of activity was again noted (Flexner and Amoss, 1924, F 29). This second period of maximal virulence was maintained for at least 4 years, for in 1922 another portion of the glycerolated material was shown to be highly active. The authors find in these 3 stages of virulence a superficial resemblance to epidemic waves. There is a possibility that the change of virulence was due to the preservations of the virus in different lots of glycerin.

A somewhat similar variation has been noted by Brodie (1932, B 31)

but, in this instance, the change in virulence seemed to have taken place more quickly. After having maintained a constant level of activity for a period, it was observed that twice as much virus (M.V. strain) was needed to produce infection in 1931, as had been required in 1930.

In a recent article, Levaditi and Hornus (1932, L 42) offer evidence to show that modifications in pathogenic activity may be due not to alterations in the biological properties inherent in the virus but to variations in the resistance of the host.

The strain, designated L P, first isolated in 1909, had maintained a constant virulence over a period of years. During the interval from November, 1931, to January, 1932, 3 specimens were found to have lost their pathogenicity for a given lot of monkeys that had been housed at the Pasteur Institute for several months. The strain proved virulent, however, for a second lot which had just been imported from Sumatra. The French workers discuss the question as to whether partial autosterilization had taken place in the cords that proved to be nonpathogenic and whether variations in the degree of autosterilization may not be seasonal. "If we admit that variations in the resistance of groups of human beings (passing from total autosterilization to absence of autosterilization through different degrees of partial autosterilization) are dependent on the environment in which these groups live, we see more reason for the seasonal variations of epidemics of infantile paralysis."

### Distribution of the Virus in the Body

**Central Nervous System.** That the human *spinal cord* contained the active agent of poliomyelitis was demonstrated when the first successful transmission of the disease to monkeys was made by inoculation with a spinal cord emulsion (Landsteiner and Popper, 1908, L 10). In the first successful transmission in series (Flexner and Lewis, first note, 1909, F 39), human lumbar cord emulsified in salt solution was used for the first inoculation and, later, emulsions of the spinal cord of the monkeys that developed paralysis. In this first series, the *cerebral cortex* also proved to be active. Römer (1909, R 21), too, used "portions of brain" as well as of cord. The early appearance of the virus in the cord after intracerebral inoculation was described by Leiner and von Wiesner (1910, L 28, II); on the fifth day of the incubation period, virus was recovered in the cord; histological lesions, however, had appeared 2 days earlier. Levaditi and Landsteiner (1910, L 47) reproduced the disease with an emulsion of the *olfactory bulbs* of an animal following submucous inoculation; Flexner and Clark (1912, F 34)



found the virus in the olfactory lobes and adjacent parts of the brain, 2 days after the nasal mucosa had been swabbed with virulent material; at this time the virus had not reached the medulla or cord. During the course of their investigations on the propagation of the virus, Fairbrother and Hurst (1930, F 6) showed that, on the third day after intracerebral inoculation, both *optic thalami* and the *pons* contained active virus, but not the cord (see *Chapter on Pathology*).

It would seem to be generally accepted that the virus may, at certain stages at least, be found in any portion of the central nervous system, but that the quantity present may vary with the location. "The virus is found wherever the typical lesions occur, *i.e.*, in the medulla, pons and brain" and "more particularly in the regions corresponding to the paralyzed limbs" (Römer, 1913, R 25). Levaditi (1922, L 34) makes the statement that the central nervous system, particularly the gray matter of the cord, is the principal reservoir of the virus. According to Amoss (1928, A 18), "practically all of the tissues of the central nervous system contain the virus, but it is apparently present in greater concentration in the lumbar and cervical enlargements of the cord and in the basal ganglia of the brain." This is in essential agreement with the findings of Fairbrother and Hurst (1930, F 6) who made a careful comparison between the microscopic lesions and the presence of the virus and found that where the nerve-cell degeneration is most severe, as in the brain-stem and the cord, the virus is present in the greatest amount. In the cerebral cortex, where the nerve-cell degeneration is slight, the virus is distributed irregularly and is inconstant in quantity. The virus disappears within a few days from the site of inoculation, thus indicating that the cerebral cortex is not a favorable location either for the development or the preservation of the virus.

The fate of the virus in the brain after intracerebral inoculation has also been studied by Jungeblut (1931, J 19). Comparison was made between the rates of disappearance from the site of inoculation in the brain of normal monkeys and of poliomyelitis convalescent monkeys. In the normal monkey, the virus was recovered from the site of inoculation during the first 24 hours; it was not recovered between 48 and 72 hours in the 3 animals tested; but at 96 hours, a sufficient quantity had apparently accumulated to transmit the infection on re-inoculation. In convalescent monkeys, the presence of the virus could not be demonstrated in either the early or later states; but in 2 instances, virus was demonstrated 48 hours after inoculation.

Quantitative studies on the distribution of the virus in the central

nervous system of monkeys have recently been made by Brodie (1932, B 31; personal communication). The infectivity of various areas of the cerebrospinal axis removed at the height of paralysis was determined by injecting increasing quantities of each area until the infective dose was determined. It was found that infection did not take place even with large quantities of the frontal pole, or of the occipital or temporal lobes. Infection was produced most easily with cord substance and then with medulla and pons respectively; the areas of the brain that were tested required still larger amounts of tissue. The results are graphically illustrated in Charts I and II which have been copied from Dr. Brodie's report. "It is evident that the spinal cord has the highest infectivity and next in order are the medulla and pons. Of a considerably lower degree of infectivity, and decreasing in virus content in the following order are: motor cortex of the uninoculated side, motor cortex of the inoculated side, mesencephalon and diencephalon, sensory cortex, cortex of the pre-Rolandic area, basal ganglia, parietal cortex, vermis of the cerebellum, lateral lobes of the cerebellum, and distal occipital cortex and pole.

"The virus has, then, an unequal and somewhat irregular distribution in the cerebrospinal axis. . . . The spinal cord, brain stem, mid-brain and diencephalon, all of which weigh less than 10 grams, constitute 92% of the total virus content of the cerebrospinal axis. The basal ganglia, cerebral cortex and cerebellum, which have a total weight of 30 grams, contain but 8% of the total virus and this despite the fact that the brain is the site of inoculation" (see *Chapter on Pathology*).

**Spinal, Gasserian and Abdominal Sympathetic Ganglia.** In their eleventh note, Flexner and Clark (F 33) made the statement that the virus had been detected in the intervertebral ganglia; in a later article, Flexner, Clark and Amoss (1914, F 36) described inoculation tests showing that active virus was present in intervertebral ganglia (human and monkey), in Gasserian ganglia (monkey), and in abdominal sympathetic ganglia (solar plexus, monkey). Lesions appear early in the intervertebral ganglia, for they have been found in monkeys in the preparalytic stage (see *Chapter on Pathology*).

**Peripheral Nerves.** Leiner and von Wiesner (1911, Z 3) were unable to demonstrate the virus either in the nerve-trunks which corresponded to the paralysis, or in the nerves after intraneural or perineural inoculation. In reference to this negative finding, Flexner (1914, F 36) remarks that "apparently the virus is not stored in the peripheral nerves



CHART I  
TITRATION OF VIRUS 113  
EIGHT MONTHS IN GLYCERINE - INCUBATION PERIOD 7 DAYS  
M.L.D. OF CORD - 0.01 CC. OF 5% SOLUTION

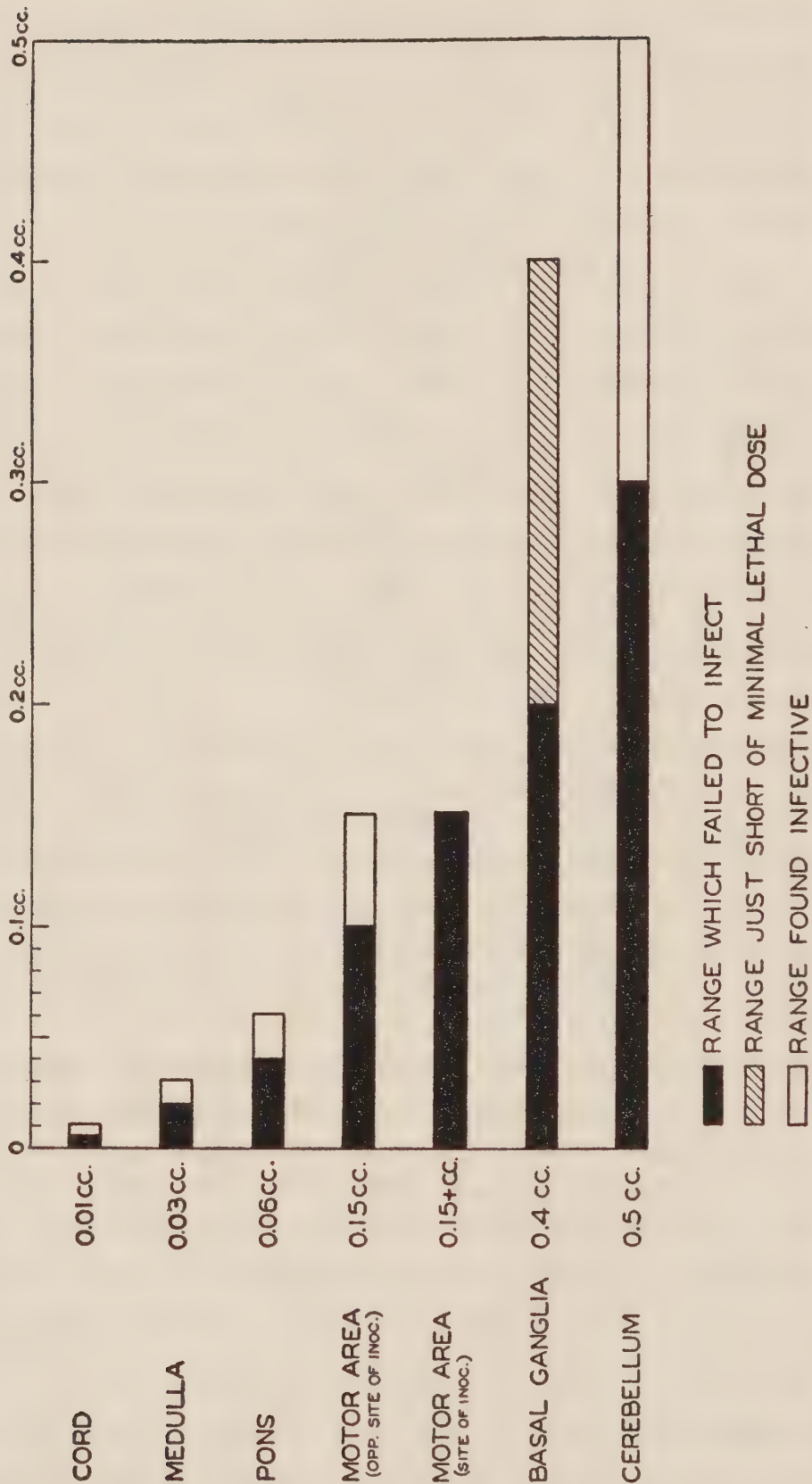


CHART I. Titration of the virus. Distribution of the virus of poliomyelitis in the central nervous system of monkeys showing relative infectivity of different levels of the cerebrospinal axis. (Brodie, Report to the Banting Research Foundation.)

# TITRATION OF VIRUS 177

FOUR MONTHS IN GLYCERINE — INCUBATION PERIOD 6 DAYS

M.L.D. OF CORD — 0.0025CC. OF 5% SOLUTION

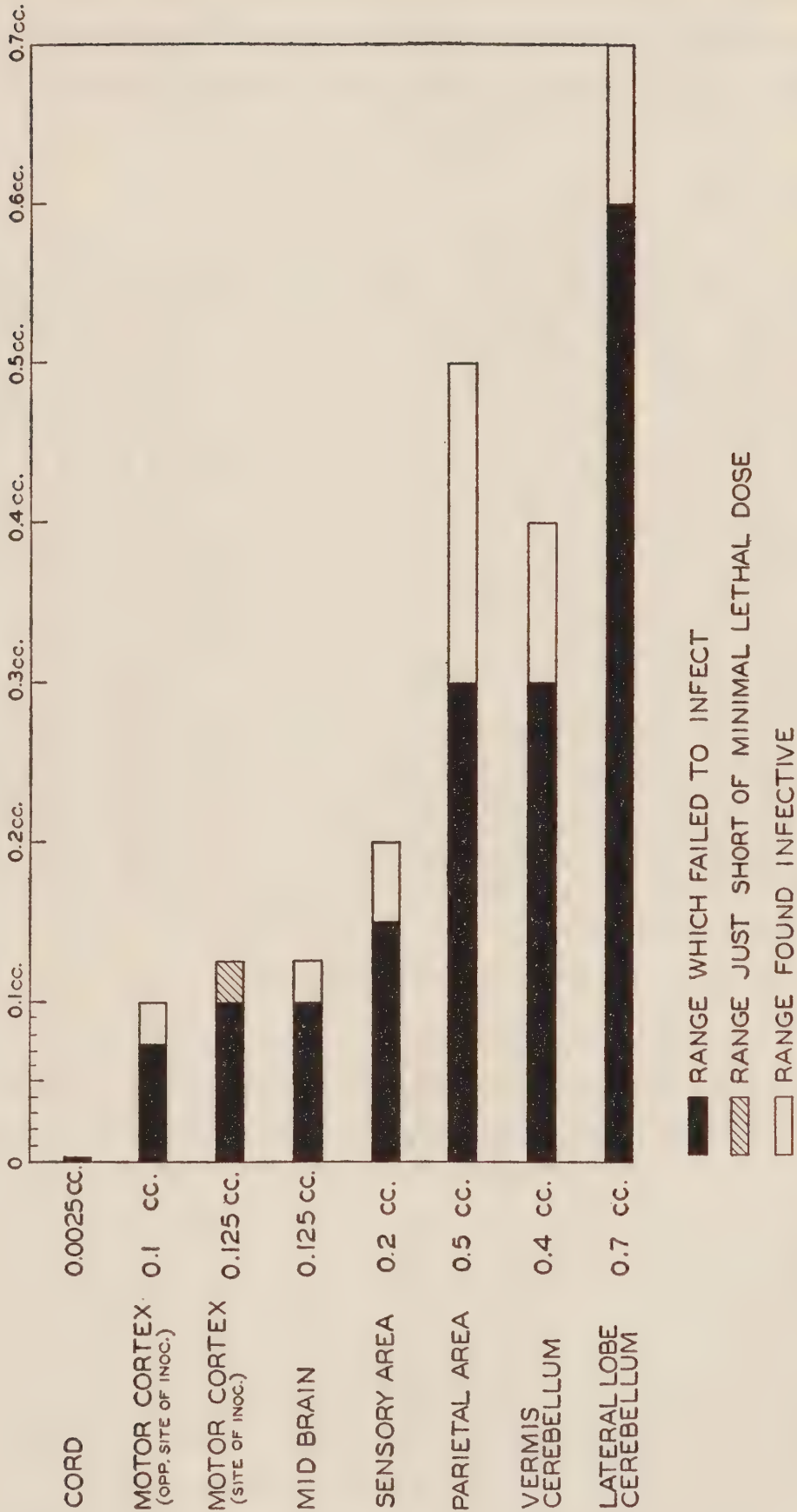


CHART II. Titration of the virus. Distribution of the virus in the central nervous system of monkeys showing relative infectivity of the cord and portions of the cerebrum and cerebellum. (Brodie, Report to the Banting Research Foundation.)



but seeks the parenchymatous nervous organs in which to multiply." More recently, however, Nicolau, Nicolau and Galloway (1929, N 26) found peripheral nerves (sciatic and brachial) infective in 2 out of 6 cases, following intracerebral inoculation.

### Cerebrospinal Fluid

**Human.** The virus of poliomyelitis has never definitely been found in human spinal fluid. This statement has been made repeatedly by many authors during the history of the experimental disease. In their first note (F 39) Flexner and Lewis refer to the fact that in 1907 they had begun attempts to transmit the disease to lower animals (including monkeys) with cerebrospinal fluid, but with negative results. Again in the eleventh note (F 33), Flexner and Clark noted that human (and monkey) spinal fluid contained no demonstrable virus at the onset of paralysis. Leiner and von Wiesner (1909, L 28, I), Strauss and Huntoon (1910, S 64), Potpeschnigg (1910, P 24), Römer (1913, R 25) also reported negative results with spinal fluid. Abramson (1917, A 2) was unable to produce the disease by intracerebral inoculation of the centrifuged sediment of fluids from 40 patients, mostly in the preparalytic stage. Reaffirmation of the failure to detect virus in human spinal fluid at any time stage of the disease has been made more recently by many workers, including Amoss (1922, 1928, A 16, A 18), Levaditi (1922, L 34), Olitsky, Rhoads and Long (1929, O 3), and Fairbrother and Hurst (1930, F 6); Brodie (personal communication, 1932) also failed to get positive results although he used 2.5 cc. from 1 case (bulbar form) and 16 cc. from another, both in the preparalytic stage.

**Monkey.** Though exceptional, positive results have been obtained with inoculations of the cerebrospinal fluids of monkeys. Flexner and Lewis (fifth note, F 43) reported in 1910 that inoculation of the spinal fluid removed from monkeys produced paralysis on intracerebral inoculation into other monkeys. In their next note (sixth note, 1910, F 44), it was stated that the fluid on the third day after intracerebral inoculation, that is, several days before the appearance of paralysis, had been shown to contain active virus. The presence of the virus in the spinal fluid of monkeys has, however, been demonstrated infrequently. Moreover, even when introduced directly into the spinal canal, the virus tends to disappear quickly from the cerebrospinal fluid. Clark and Amoss (1914, C 13) found that when the virus was injected directly into the subarachnoid space, it could be demonstrated there

48 hours after the injection, but could not be detected in the sixth day when the first symptoms of the disease developed. These authors concluded that the virus escaped from the subarachnoid spaces, partly into the central nervous tissues and partly into the general circulation. Flexner and Amoss (1914, F 21) were unable to demonstrate the virus in the spinal fluid removed 48 and 72 hours, respectively, after intravenous injection of a very large dose. But fluid removed 96 hours, and 19 days after injection (in this instance at the onset of paralysis, due to delayed infection) contained active virus as shown by inoculation tests. In no other instance had the virus been found in the spinal fluid at the onset of paralysis.

The relative infrequency of such positive results has recently been emphasized by Olitsky, Rhoads and Long (1929, O 3) and by Fairbrother and Hurst (1930, F 6). The former authors make the comment that "recent tests with the spinal fluid . . . have again shown that the fluid is free from virus." Although their examinations were made at all stages of the disease, Fairbrother and Hurst were able, in only 1 of the 6 tests made, to detect the virus in the spinal fluid after intracerebral inoculation and, in this case, they had reason to believe that the injection was made not into the substance of the brain but directly into the lateral ventricle. Subsequently, however, Hurst (1930, H 40) found active virus in the fluid in 3 out of 10 examinations following intrasciatic injection, and, in 1 instance (H 43), virus persisted in the spinal fluid 5 days after intrathecal inoculation.

## Blood

**Human.** The virus has not been detected in human blood, even when large amounts have been used (Leiner and von Wiesner, 1909, L 28, I; Strauss and Huntoon, 1910, S 64; Flexner and Clark, 1911, F 33; Clark, Fraser and Amoss, 1914, C 14; Flexner, 1915, F 14; Amoss, 1928, A 18).

**Monkey.** Flexner and Lewis (1911) were able to show the presence of the virus in monkey's blood (Flexner and Clark, eleventh note, F 33) if large quantities (25 cc.) were withdrawn at the height of the disease. Leiner and von Wiesner (1911, Z 3) also reported success in 1 out of 5 tests with blood drawn at different stages of the disease; in this instance, inoculation had been by the combined intracranial and intravenous method. Clark, Fraser and Amoss (1914, C 14) were successful in finding virus in the blood in 1 out of 10 instances; in this case, the



blood was removed at the beginning of the paralysis on the seventh day following intracerebral inoculation. After intravenous injection of an overwhelming quantity of an active filtrate, the virus was found to persist in the blood for 72 hours, but had disappeared 10 days after the injection at the onset of the paralysis.

Thompson (1930, T 8) attempted to determine whether the virus could be detected in the blood, by separating the white cells, to which the virus is fixed, from the antibody containing serum. Specimens of blood were taken from 3 different monkeys at 4 stages of the disease. Intracerebral injections of the cells from these specimens into other monkeys produced no evidence of poliomyelitis. Thus, the virus did not appear to be present in any greater quantity in concentrated cell suspensions than in whole blood.

### Lymph Nodes

**Mesenteric.** In their sixth note, Flexner and Lewis (1910, F 44) reported the presence of the virus in human mesenteric lymph nodes. Römer and Joseph (1910 R 30) and Leiner and von Wiesner (1910, L 28, IV) also found active virus in the mesenteric nodes taken from monkeys. As Leiner and von Wiesner's animals had been inoculated intracerebrally or intraneurally, they concluded that the virus had penetrated these nodes secondarily from the cord, either by the hematogenous or the lymphogenous route. Kling, Levaditi and Lépine (1929, K 13), on the contrary, reported that the mesenteric nodes from 2 of 3 animals infected through the digestive tract, were virulent, while those from another animal inoculated intracerebrally were not. These authors expressed a belief in a lymphatic spread of the virus, in particular when it enters through the digestive mucosa (see *Portal of Entry and Pathogenesis*).

**Other Lymph Nodes.** After subcutaneous injection of virus, the regional lymph nodes (axillary and inguinal) have been shown to be virulent (Flexner and Lewis, fourth note, 1910, F 42). Virus was demonstrated in the cervical (and mesenteric) but not in the inguinal nodes, following intracerebral and intraneural inoculation, in about one-half of the cases examined (Leiner and von Wiesner, 1910, L 28, IV; Z 3); nor were inguinal nodes, removed after testicular inoculation, virulent (Jungeblut and Thompson, 1930, J 29). Levaditi, Schmutz and Willemain (1930, L 51) also failed to find inguinal nodes (human) infective, 5 days after onset of the disease.

**Tonsils and Mucous Membranes of the Nasopharynx.** "The only

regions outside the nervous system in which it (the virus) can be found with any regularity are the tonsils and nasopharyngeal mucosa" (Fairbrother and Hurst, 1930, F 6). Filtrates of the nasopharyngeal mucous membranes of monkeys inoculated with virus intracerebrally or intraspinally were early found to be infective for other monkeys (Flexner and Lewis, fifth note, 1910, F 43); Leiner and von Wiesner, 1910, L 28, IV; Z 3). The presence of the virus was also demonstrated in the tonsils and attached pharyngeal membrane removed after death in human cases (Landsteiner, Levaditi and Pastia, 1911, L 9); Flexner and Clark, eleventh note, 1911, F 33) and in monkeys inoculated intracerebrally (Landsteiner, Levaditi and Danulesco, 1911, L 7). Thus it was suggested that the nasopharynx might be a path of elimination as well as a portal of entry of the virus.

Although some authors have been unable to detect the virus with regularity in these locations (Leiner and von Wiesner, L 28, IV; Z 3; Levaditi and Danulesco, L 39), the finding itself has been confirmed repeatedly (Flexner and Clark, ninth note, 1911, F 31); Osgood and Lucas, 1911, O 4; Thomsen, 1912, T 10; Pettersson, 1912, P 12; Lucas and Osgood, 1913, L 73; Flexner and Amoss, 1919, F 27; Levaditi, Schmuts, and Willemin, 1930, L 51).

### Nasopharyngeal Secretions or Washings

**Monkeys.** The supposition that the virus might be excreted by way of the nasopharynx received support when Landsteiner, Levaditi, and Danulesco (1911, L 7) demonstrated the presence of the virus in the nasal secretions. A cotton tampon was placed in the nostril of an infected monkey (inoculated intracerebrally). The absorbed secretion was used to infect a second monkey by combined intracerebral and intraperitoneal inoculation. Thomsen (1912, T 10) was able to produce infection by simply rubbing the nasal secretions obtained from a monkey dying after intraperitoneal inoculation on the nasopharynx of a second monkey.

#### Human Cases

**Patients with the Disease or After Death.** Kling, Pettersson and Wernstedt (1911, K 16, S 67) were the first to bring forward evidence that nasopharyngeal washings of *human cases*, obtained either during the acute stage of the disease or after death could be used to produce the typical disease in monkeys. In addition, these authors reported positive results when they used washings from abortive cases, several months



after the acute illness. The results in this group of experiments, however, have been questioned by other investigators (Flexner, Clark and Fraser, 1913, F 38; Flexner and Amoss, 1919, F 27) who do not accept the criteria of the experimental disease as described by the Swedish workers. Kling, Pettersson and Wernstedt, themselves, make the admission (S 67) that "in several cases which we have regarded as positive, we have not found those changes which have hitherto been considered as the most characteristic of acute poliomyelitis. . . . Instead we have found a characteristic change in the cells of the supporting tissue. . . . Also we have found a considerable degeneration of the ganglion cells. . . . We consider these changes also to be due to, and to a certain degree to be characteristic of the effect of the virus of infantile paralysis" (see also Kling and Levaditi, 1913, K 12). Flexner and Amoss (1919, F 27) were not able to confirm the existence of such an atypical form of the experimental disease, attributed by Kling and his associates to a less virulent virus or to washings containing too small a quantity of virus.

In a single case of the nonparalytic type, DuBois, Neal, and Zingher (1914, D 24) were able to transmit the disease to a monkey by the intraperitoneal injection of nose and throat washings, obtained 17 days after the onset of the disease. Passage to a second monkey was successful but the series could not be carried further.

Recently Paul and Trask (1931, P 5) obtained positive results with oral washings in 2 out of 12 cases of minor illness (abortive cases). These came from families or groups in which there had been another case of recognizable poliomyelitis. It is, perhaps, important that these 2 successful attempts to isolate the virus were from the 6 cases in which the washings were made early in the disease, that is, on the first or second day of the illness. They were unable to obtain the virus from the nasopharyngeal washings from cases taken later in the disease.

**Healthy contacts.** The presence of the virus in the nasopharynx of healthy persons in intimate contact with the disease, has been demonstrated by Flexner, Clark and Fraser (1913, fourteenth note, F 38) and later by Kling and Pettersson (1914, K 15). In the first study, the nasopharyngeal washings of the parents of a 4-year-old child, acutely ill with the disease, proved virulent. In the second, washings of the nasopharynx of the other 3 members of the patient's family were concentrated from 1 liter to about 75 cc. Combined intracerebral and intraperitoneal inoculation of the filtrate produced typical lesions in a monkey. Thus the possibility of *passive human carriers* has been demonstrated.

**Active Carriers: Persistence of the Virus in the Nasopharynx.**

The length of time that active virus may persist either in the tissues or in the secretions of the nasopharynx is an important epidemiological point. Leiner and von Wiesner (1910, L 28, IV; Z 3) were successful in transmitting the disease when the nasopharyngeal mucosa was removed on the second day of the illness in monkeys, but unsuccessful when it was removed on the fifth or sixth days. Osgood and Lucas (1911, O 4), however, found that nasopharyngeal mucous membrane of a monkey contained active virus  $5\frac{1}{2}$  months after the acute stage—thus longer than it had been shown to survive in the central nervous system. Flexner and Clark (1911, F 31) demonstrated virus in a similar location more than 4 weeks after the paralysis, although the spinal cord of the same animal did not prove to be infectious.

In 1919, Flexner and Amoss (F 27) reported a series of tests with tonsils and pharyngeal mucosa removed at autopsy and with tonsils and adenoids removed at different intervals after the acute attack. From the first set of experiments, the authors concluded that the nasal and pharyngeal mucosae of persons dying during the first week or ten days of acute poliomyelitis probably regularly contain the virus; but that corresponding tissues removed surgically, that is, later in the disease, rarely, if ever, contain sufficient virus to produce infection in a monkey. Thus “the period of greatest infectivity of patients would appear to be early in the disease.”

Reference has been made above to the reported demonstration of the virus in the nasopharyngeal washings of abortive and convalescent cases and of carriers (Kling, Pettersson and Wernstedt, 1911, K 16). Lucas and Osgood (1913, L 73) described recovery of the virus from the nasopharyngeal secretions of a human carrier 4 months after the acute stage of a second attack of poliomyelitis, or 2 years and 7 months after the first attack. Second attacks of the disease, however, are so infrequent that no general conclusions can be drawn from this case.

Taylor and Amoss (1917, T 1) brought forward evidence to show “that a proved carrier of the virus may come down with acute poliomyelitis.” They observed 4 children in one family, all with symptoms of poliomyelitis in varying degrees. The virus was detected in the nasopharyngeal washings of 2; in 1 case the material was obtained 3 days after what was considered an abortive attack; in the other, the test was made 5 days before the initial symptoms appeared; paralysis developed subsequently. It may be questioned whether the subject in this instance was a carrier or whether the test may not have been made early in the incubation period of the disease.



It has been pointed out by Flexner and Amoss (1919, F 27) and again, more recently, by Levaditi, Schmuts, and Willemin (1930, L 51) that negative results with dilute, filtered washings of the nasopharynx are without real significance, especially since virus obtained immediately from human beings often fails to incite infection in monkeys. The undoubted positive evidence, as in certain instances described above, is therefore all the more convincing.

**Tracheal Secretions and Mucous Membranes.** Demonstration of the virus in the secretions and in the mucous membranes of the trachea of human beings dying with poliomyelitis has been reported by Kling, Pettersson and Wernstedt (1911, K 16, S 67) and by Kling and Levaditi (1913, K 12).

**Intestinal Secretions and Mucous Membranes.** The same authors (Kling, Pettersson and Wernstedt, K 16, S 67) have reported the presence of the virus in the intestinal secretions and mucosa of persons after death and in the secretions of abortive cases and carriers during life.

**Feces.** The question of the possible occurrence of the virus in the feces is important epidemiologically and was early investigated. Levaditi and Landsteiner (1910, L 46) and Leiner and von Wiesner (1910, L 28, IV) were unable to detect the virus in the feces of monkeys with the experimental disease.

Positive results were reported by Kling, Pettersson and Wernstedt (K 16; S 67) in monkeys inoculated with the filtrates of stools of acute cases (human). Their findings in these experiments are, however, open to the same objection as in the tests made with nasopharyngeal washings. Levaditi, Schmuts, and Willemin (1930, L 51) make special note of the fact that, in the 1930 epidemic in the Bas-Rhin the virus was rarely found either in nasopharyngeal secretions or in feces, thus differing from the previous results of the Swedish workers as well as from those of Kling and Levaditi (1913, K 12).

In recent tests with monkeys, Clark, Schindler and Roberts (1930, C 16) reported that in only one set of 6 experiments, the feces obtained after feeding large volumes of virus afforded an inoculum with which the disease was produced experimentally. Moreover the concentrate of feces from acute cases gave negative results in the three groups studied. These authors concluded that the virus does not commonly pass through the intestinal tract of monkeys in an infective form.

Subsequently, with a more active strain of virus, Clark, Roberts and Preston (1932, C 15) took up again the problem of virulent feces. The

*M. Cynomolgus* was used as Kling, Levaditi and Lépine have suggested that this species is more susceptible to the virus of poliomyelitis. Filtrates of the feces were concentrated *in vacuo* and then dialyzed to remove excess salts. Infective quantities of virus were demonstrated in the feces of 2 animals in which 10 cc. of active brain cord suspension had been introduced into a loop of the small intestine and in the feces of 5 out of 8 animals that had been fed various forms of active virus for periods of 1 to 4 days. The authors, were, however, unable to demonstrate the virus in the feces of animals suffering from the disease.

Levaditi, Kling and Lépine (1931, L 43) also examined the feces of a monkey infected by mixing virus with the food. The specimens obtained 24 or 48 hours after ingestion by mouth proved virulent but those obtained on the eighth day (during the incubation period) and on the thirteenth day (after paralysis) were not (see under *Routes of Inoculation—Gastro-intestinal*).

Recently Toomey (1932, T15a) has reported evidence of a "specific toxic factor" in the stools and urines of poliomyelitis patients. It was found that "subcutaneous injection of urine specimens or saline emulsions of stools obtained from patients ill with poliomyelitis brought about the death of guinea pigs in greater numbers than similar specimens obtained from normal individuals." The possible relation of this toxic factor to the virus is not discussed.

**Other Locations.** Landsteiner and Levaditi (1909, L 5) demonstrated the virus, by inoculation tests, in the *salivary glands* (parotid and submaxillary) and suggested that the virus might be eliminated through the saliva. Römer (1910, R 22) and Leiner and von Wiesner (1910, L 28, IV) were unable to confirm this finding. Leiner and von Wiesner (L 28, IV) were also unable to detect the virus in the spleen, kidneys, urine, or bile. According to Levaditi (1922, L 34) the virus is not found in the liver, kidney, bonemarrow, or spleen. It was, however, detected by Flexner and Amoss (1914, F 22) in the spleen and bonemarrow, following intravenous injection, but not in kidneys, spinal cord, or brain. Under these conditions, the virus had survived for 17 days in the spleen without reaching the central nervous system but the virulence had been diminished, apparently by the action of the spleen.

### Persistence of the Virus in the Body

**Nasopharynx.** The persistence of the virus in the nasopharynx has been considered (see *Active Carriers*).

**Spinal Cord.** In one instance, Leiner and von Wiesner (1910, L 28,



IV) were able to detect the virus in the cord 24 days after the inoculation; and Römer (R 25) found cord substance virulent after 33 days. Levaditi and Landsteiner (1910, L 46), however, obtained positive results with the cord of an animal that had been sick 4 days, but negative results with others removed 9 and 45 days after onset of symptoms and concluded that the virus disappears from the central nervous system when the acute stage is past. By cataphoresis, Olitsky, Rhoads, and Long (1929, O 2) detected virus in the cord 23 days after the infection but Levaditi and Lépine (1931, L 49a) were unable to recover it by this method 35 and 86 days after inoculation.

Jungeblut (personal communication) found the spinal cord enlargements negative for virus in 2 instances, 4 and 6 weeks, respectively, after the onset of symptoms; and Brodie (B 31) was unable to produce infection with cord tissue removed 3 weeks after the height of paralysis. Brodie also determined the rate at which infectivity disappears from the cord after the height of paralysis; the amount of cord substance required to produce infection was estimated at various intervals. It was found that the infectivity diminished with regularity, so that at 2 days after the height of paralysis, it was only one-fourth, at 4 days one-fortieth, at 6 days one-sixtieth, and at 8 days one-eightieth of the original amount.

It would seem from the above that the virus is seldom present, at least in detectable amounts, after the third or fourth week. That it may persist for a longer period, however, has been demonstrated in the human disease, in one instance (Krauspe, 1928, K 35; Hässler, 1929, H 1). The patient, a 14 year old boy, had recovered from poliomyelitis. On the ninety-ninth day, pneumonia developed, with death in 24 hours. Histologically, the cord showed the usual processes of repair with only isolated areas of recent infiltration. A monkey, inoculated with an emulsion of the cord, developed the typical experimental disease (see also *Chapter on Pathology* for persistent lesions).

**Monkey Testicle.** Jungeblut and Thompson (1930, J 29) have shown that survival of the virus in this tissue is exceptional, even for short periods of time.

### Routes of Inoculation

**Intraperitoneal.** The first successful transmissions of the experimental disease to monkeys were by this route (Landsteiner and Popper, 1908, L 10; Knoepfelmacher, 1909, K 18). These authors were, however, unsuccessful in their attempts at serial transmission by this

method and it was soon shown that inoculation by this route, alone, was a somewhat uncertain procedure (Leiner and von Wiesner, 1909, L 28, I; Strauss and Huntoon, 1910, S 64) and one for which large doses were necessary (Amoss, 1922, A 16).

**Intracerebral.** By this method, transmission in series was first accomplished (Flexner and Lewis, first note, 1909, F 39). This route of inoculation is now generally accepted as the most effective, and is the one so commonly adopted for routine experimental work. Intracerebral injection requires the least amount of virus (Amoss, A 18); 0.5 cc. of a 5 per cent cord emulsion or of a virulent filtrate is a frequent dosage (Römer, R 25; Fairbrother and Hurst, F 6).

Amoss (1922, A 16) has stated that if the virus is adapted to monkeys, very small amounts may suffice, for example, 0.001 cc. of a Berkefeld filtrate of a 5 per cent suspension of central nervous system tissue ( $\frac{1}{500,000}$  gram of nervous tissue). This inoculation is usually made under ether anesthesia through a small trephine opening (Flexner and Lewis, first note, 1909). The virus is injected with a needle. Römer (R 25) performed the operation over the central gyri. Fairbrother and Hurst (F 6) made the injections in the parieto-occipital region; and Schultz and Gebhardt (S 13) have used the frontal lobe.

**Intraneural.** Infection by way of the peripheral nerves takes place readily. Intraneural or perineural inoculation was early reported by Flexner and Lewis (1909, F 40), Landsteiner and Levaditi (1909, L 5), Leiner and von Wiesner (1910, L 28, II; Z 3), and Marinesco (1911, M 18). Flexner and Lewis (F 40) observed that, if the virus was injected into the sheath of the sciatic nerve, lesions with resulting paralysis developed first on the side inoculated, and later on the opposite side. In one instance, however, it was thought (Flexner, Clark and Amoss, 1914, F 36) that the virus had ascended by the lymphatics to the cervical cord with consequent paralysis in an arm before paralysis could be demonstrated in the leg of the inoculated side.

Intrasciatic inoculation was considered by Flexner and Amoss (1917, F 24) to constitute an "uncertain portal of entry." Fairbrother and Hurst (1930, F 6, H 40), however, found that infection invariably resulted with this method, if the nerve fibers were traumatized to a certain extent. The incubation period was shorter than with intracerebral inoculation. Paralysis always began in the leg of the inoculated side, followed rapidly by involvement of the opposite leg, then by weakness of the arms and face, with death within 30 to 48 hours.

While making inoculations into the peripheral nerves, Demme (1930,



D 10) found that the nearer the site of inoculation to the central nervous system, the more rapid the development of the paralysis; for the sciatic nerve, the incubation period was 5 days, for the median, 4 to 6 days, while for the facial, it was only 3 days.

**Intraocular.** Landsteiner and Levaditi (1909, L 5) introduced virus into the anterior chamber of the eye of a monkey. Infection followed after an incubation period of 7 days.

Similar experiments described by Flexner and Amoss (1914, F 22) showed that the virus penetrated the retina without injuring it. In one instance the ophthalmic ganglion on the inoculated side showed a diffuse cellular infiltration.

**Intraspinal and Intracisternal.** Successful inoculation by the intraspinal route was early reported by Flexner and Lewis (1910, F 43), Neustaedter and Thro (1911, N 16) and Römer (1913, R 25). According to Clark and Amoss (1914, C 13), infection was accomplished by this method without difficulty, provided an active virus was used and larger doses than those necessary for intracerebral inoculation.

Injection of the virus directly into the cisterna has been employed (Flexner and Rhoads, 1929, F 52; Hurst, 1932, H 43) in order to avoid trauma to the brain tissues. With an active virus, infection follows regularly and without prolongation of the incubation period.

**Intravascular.** Although Leiner and von Wiesner (1909, L 28, I) were unable to produce poliomyelitis by intravenous injection, positive results were reported by Flexner and Lewis (1909, F 40, F 47), and by Landsteiner and Levaditi (L 34). But "it is only when overwhelming quantities of an active virus are injected into the blood that paralysis results" (Clark, Fraser and Amoss, 1914, C 14). Production of an aseptic meningitis by the intraspinal injection of normal horse serum (Flexner and Amoss, 1914, F 22) or even of normal monkey serum, isotonic salt solution, or Ringer's, or Locke's solution (Flexner and Amoss, 1917, F 24) facilitated infection by rendering the choroid plexus more permeable to the virus (see also *Mechanisms of Defense*). Demme (1930, D 10) has referred to an incubation period of 2 days following intravenous inoculation with a virulent strain, but does not give the dosage.

Virus injected centripetally (into the carotid artery) did not produce infection any more readily than when injected into the veins (Jungeblut, personal communication; Landsteiner, Levaditi and Pastia (1911, L 8) had also been unsuccessful with this method.

**Peripheral Lymph Nodes.** Infection developed as a result of the

injection of the virus into the regional lymph nodes. This indicated to Leiner and von Wiesner (1910, L 28, II) the possibility of transmission by way of the lymphatic system.

**Cutaneous.** Cutaneous inoculation by inunction of the virus after scarification was attempted by Landsteiner and Levaditi (1909, L 5) and by Leiner and von Wiesner (1910, L 28, II; Z 3) but with negative results.

**Subcutaneous.** Success in producing the experimental disease by subcutaneous injection was reported by Flexner and Lewis in their third note (1909, F 41). Amoss (1922, A 16), however, has stated that infection by this route can be obtained only with difficulty. Neustaedter and Thro (1911, N 16) used a combined intraspinal and subcutaneous method. Attempts at experimental immunization by this route have shown that infection may frequently take place (see *Section on Active Immunization*).

**Intracutaneous.** Immunization experiments have shown that infection may follow injection of virus by this route especially in those instances where sensitization has been produced. However, when a potent virus is used (such as the M.V. strain), infection may be obtained consistently by this route (Brodie, personal communication; B 31) with an average incubation period of 8 days. Infection is more certain, according to Brodie, than by the intranasal route and all trauma to nervous tissue is avoided. The total amount of virus to be used is injected in one bleb; 15,000 to 20,000 times as much infective cord material was required as for a successful intracerebral inoculation.

**Intrapleural.** No infection resulted from the intrapleural injection of immunizing doses of virus in the 3 monkeys tested (Jungeblut and Hazen, 1930, J 23).

**Intranasal.** This method of inoculation has been of especial interest because of the possible relation to the human route of infection. Intranasal inoculation of monkeys has been accomplished by spraying a virulent emulsion on the cocainized mucous membrane, by gently swabbing the nasal mucosa with virus emulsion, or by placing a tampon containing virus in the naris (Leiner and von Wiesner, 1910, L 28), by injecting the virus under the nasopharyngeal mucosa (Landsteiner and Levaditi, 1910, L 47, L 6), and by applying the virus to the scarified mucous membrane (Flexner and Lewis, F 44). Landsteiner and Levaditi concluded that failures were due to the barrier presented by an intact mucous membrane but Levaditi and Danulesco (1912, L 37a) found that the virus easily penetrated the nasal mucosa, even without prelimi-



nary irritation. Penetration through the tonsils was effected less readily.

Infection is not always readily accomplished, however. "The percentage of successful inoculations by the nasal route is smaller than by the brain or intracerebral route" (Flexner and Amoss, F 28). Fairbrother and Hurst (1930, F 6) have also found that "infections resulted very inconstantly;" and Howitt (1932, H 36) obtained positive results with intranasal instillations in only 53 per cent of the animals treated.

Flexner and Amoss (F 28) have described experiments in which they studied "the conditions underlying the states of susceptibility and refractoriness" to infection by this route. It appeared that the nasal mucosa of some animals had the power to render the virus ineffective while that of others did not; and that the virus survived for only a brief length of time on an effective, but for an undetermined period on an ineffective membrane. Antiseptics (chloramine-T and dichloramine-T) applied to the nasal mucosa did not prevent infection. Levaditi and Danulesco (1912, L 40) had also found that local antiseptics, even though they had microbicidal powers *in vitro*, were ineffective in preventing penetration of the virus through the nasal mucous membrane. Flexner and Amoss suggested that such chemicals might even be objectionable because of their unfavorable effect on the destructive power of the membrane. These authors concluded that "the normal nasal mucosa, is, therefore, an invaluable defense against infection with the virus of poliomyelitis; and the number of healthy and chronic carriers of the virus is probably determined and kept down through the protective activities of this membrane."

According to Demme (1930, D 10), infection resulted only when the nasal mucosa had been injured; rubbing the virus in the nose produced slight bleeding; infection then followed after an incubation period of 10 days. Demme raises the question as to whether the upper respiratory symptoms, which often precede poliomyelitis, are really the first symptoms of the disease, or whether they are independent diseases which make possible the entrance of the virus into the organism.

Flexner (1931, F 20a) has recently called attention to the great regularity with which infection can be induced in monkeys by simply dropping the virus into the nares for several successive days. The incubation period is 10 to 15 days after the first instillation or 7 to 10 days after the last. Flexner comments that this is the only experimental method of inoculation through an external portal which gives reliable results.

**Intratracheal.** Leiner and von Wiesner (1910, L 28, III; Z 3) reported success by injection of virus into the exposed trachea, but Flexner and Lewis (1910, F 47) were unable to produce infection by this route.

**Gastro-intestinal.** Especial interest attaches to attempts at inoculation by this route because of the possibility that the gastro-intestinal tract may be a natural portal of entry of the virus. Infection by this path has been accomplished by certain authors, though usually only with difficulty, while in the hands of other investigators it has proved unsuccessful.

Leiner and von Wiesner (1910, L 28, II; Z 3) administered the virus by two methods following a preliminary starvation period of 24 to 48 hours and intraperitoneal injection of opium to reduce intestinal peristalsis. Two monkeys received centrifuged cord emulsion, in repeated doses, by stomach tube; 1 developed the marantic form of the disease, confirmed by histological examination. In 3 animals, the virus was incorporated in a fold of the small intestine; typical paralytic symptoms were observed in 1.

Lentz and Huntemüller (1910, L 30) reported success by the intrastomachic route but gave no experimental details.

Kling, Levaditi, and Lépine (1929, 1931, K 13; L 43) have recently reported positive results. These authors found the *M. cynomolgus* more susceptible to infection by this route than the *M. rhesus*. An extremely virulent virus was used. Cord emulsion was given by stomach tube to 2 *cynomolgus* monkeys; another ingested contaminated water; death occurred suddenly in each case; the diagnosis of poliomyelitis was made by histological examination and by animal passage. Two *rhesus* monkeys survived without symptoms after 3 ingestions of contaminated water. One of these showed no immunity to intracerebral inoculation. One *M. cynomolgus* also developed the disease with typical lesions after the ingestion of contaminated food, and another after introduction of the virus into a fold of the intestine. This last experiment, in the opinion of the authors, excluded the possibility of accidental infection by contact with the upper respiratory passages.

According to Demme (1930, D 10), infection could be produced by this route, as by the nasopharyngeal, only after injury to the mucous membrane. Virus was administered to 2 animals (species not stated) by stomach tube. One had received saponin with the food daily for some days preceding the inoculation, with a resultant diarrhea; the other had received no preparatory treatment; the former developed poliomyelitis after an incubation period of 14 days.



In another instance, recently described (Saddington, 1932, S 3), a *Macacus cynomolgus* developed the experimental disease after having received 6 daily feedings of 30 cc. of virus-infected milk. These were administered by mouth with a medicine dropper. The first symptoms appeared 11 days after the last feeding. Microscopic examination revealed lesions typical of poliomyelitis.

On the other hand, Landsteiner and Levaditi (1909, 1910, 1922, L 5, L 46, L 6, L 34) were unable to produce infection either in lower monkeys or in a chimpanzee. The results were negative, whether the virus was given by stomach tube or ingested with milk, or given with milk by rectum. Nor had immunity developed as shown by subsequent intracerebral inoculation.

In the 2 instances described by Leake (1918, L 18) feeding of virus mixed with banana failed to produce the disease; portions were distributed over a period of 4 days. Morphine sulphate was also administered subcutaneously. On subsequent intracerebral inoculation, 1 of the monkeys thus treated failed to come down with the disease at the first test, but succumbed to the second inoculation after an incubation period of 10 days. The question was raised as to whether the animal had been rendered partially immune by the feedings.

Amoss (A 18) fed monkeys large amounts of virus over a period of 42 days, following the procedure of Leiner and von Wiesner. The results were negative even when all possible mesenteric lymph nodes had been removed. At the close of the experiment, the animals were susceptible to intracerebral inoculation. Schultz (1929, S 12) could produce neither infection nor immunity by feeding virus with milk, after a short fasting period.

Thompson (1930, T 8) has also been unable to produce infection; virus emulsion was given by stomach tube after fasting, and irritation of the gastro-intestinal tract by bile. The tests for immunity, however, were not decisive. One monkey developed an extremely mild poliomyelitis on intracerebral inoculation; 2 others survived a first test; 1 of these also survived a second test but showed a mild and delayed weakness of the legs.

Although large quantities of a brain-cord suspension were employed, Clark, Schindler and Roberts (1930, C 16) were unsuccessful in producing poliomyelitis in 3 *Macacus rhesus* monkeys. Two animals received 20 to 25 cc. of the suspension by stomach tube, once in 5 days, for a period of 14 weeks, making a total of 310 cc.; another was similarly treated for 8 weeks and received a total of 215 cc. None of the monkeys

showed evidence of infection and subsequently all came down typically after an intracerebral inoculation of virus.

Attempts have been made to confirm the positive results obtained by Kling, Levaditi and Lépine (1929, 1931, K 13, L 43) with other species than the *Macacus rhesus*. Jungeblut and Thompson (1930-1931, J 30) were unsuccessful with a baboon, the 1 animal tried. Although they used an active strain, Clark, Roberts and Preston (1932, C 15) failed to produce poliomyelitis in *Macacus cynomolgus* monkeys either by feeding large quantities of virus or by the introduction of 10 cc. of virus into a loop of the small intestine. To these authors, some of the work of the French group seemed "inconclusive;" the clinical picture was not typical as the animals died suddenly without previous symptoms; the microscopic lesions were not described; and in only 1 of the 3 instances was mention made of reinoculation. Clark and his associates emphasize the fact that "in attempting to produce poliomyelitis by feeding, one must be aware of the possibility of infection through the tonsils or even by the nasal route, through regurgitation of the virus." Even when the stomach tube is used, the nasopharynx may be infected during the withdrawal of the tube. "It may well be that the tonsils are frequently a primary site of infection both in milk-borne and droplet-infection cases." (Discussion of the question of the natural portal of entry of the virus is found in the *Chapter on Pathology*.)

### The Experimental Disease

**Susceptibility of Monkeys.** Monkeys are the only animals definitely known to be susceptible to poliomyelitis. It is, however, recognized that even monkeys possess a certain natural refractory state which varies according to the species (Levaditi, L 34). Varieties of old world monkeys seemed to Flexner and Lewis (1910, F 47) more susceptible than those of the western hemisphere. Phylogenetically the catarrhine or old world species are more closely related to man than the platyrrhine or new world monkeys. Judging from the dose of virus necessary to produce infection, Thomsen (1912, T 11) concluded that the *Macacus cynomolgus* was more susceptible than the *Macacus rhesus* or *sinecus*; the *Macacus rhesus* is, however, more frequently employed in experimental work in the United States than any other variety. Other species used more or less extensively are: *M. nemestrinus*, *Cercocebus fuliginosus*, *Cercopithecus callitricus*, *Papio babium*, and in some instances ringtail monkeys of the genus *Cebus*, including *Capuchinus*



(Flexner and Lewis, F 47); also *C. ruber* and a Tota monkey (Römer, R 25); *M. callitrichus*, *Cynocephalus hamadryas*, and the chimpanzee (*Troglodytes niger*) (Levaditi, L 34).

Kraus and Kantor (1917, 1918, K 31) also considered monkeys of the new world definitely less susceptible; in their hands, the Paraguayan genus (*Cebus*) proved completely refractory. The results obtained by Jungeblut and Engle (1932, J 21) are in agreement with those of the South American Workers. The mechanism of this resistance is discussed under *Distribution of Neutralizing Substances in the Animal Kingdom* in the *Chapter on Resistance and Immunity*.

Even within a given species, and with a potent virus, certain animals may prove more refractory than others. Of 83 monkeys in their first series, Flexner and Lewis (1910, F 47) found that 6 failed to develop paralysis as a result of intracerebral inoculation. A smaller proportion, 7 out of 350, of those tested by Harmon, Shaughnessy and Gordon (1931, H 14) resisted a primary inoculation, though only 1 proved totally refractory. These authors termed the above cases "missed infections," because the failure occurred in a series of experiments in which a certain dilution of virus produced no paralysis, although the preceding and succeeding monkeys, inoculated with a lower and a higher dilution, became typically paralyzed. Reinoculation not infrequently, however, results in infection, even though the first injection has been ineffective (Harmon, Shaughnessy and Gordon, S 32, H 14; Flexner, F 20) (see also under *Strains*).

Recent workers, however, are reporting fewer missed infections than formerly. In Jungeblut's experience (personal communication) only 1 control out of 125 failed to develop the disease, and this 1 succumbed to a subsequent inoculation. Brodie (personal communication) has had no failures and attributes this to the fact that only those portions of the central nervous system shown to be most infective are used in preparing the material for inoculation.

Leiner and von Wiesner (1909, L 28, I; Z 3) believed that the age of the monkey affected in some measure the success of the inoculation. Their negative results occurred usually in experiments in which large powerful animals had been used. Krause and Meinicke (1910, K 34), and Levaditi (1922, L 34) have also stated that young monkeys are more susceptible than old ones. Although occasional successful inoculations in older animals have been reported (Ionesco-Mihaiesti and associates, I 3), the results of the recent experimental work by Jungeblut and Engle (1932, J 21) referred to above would tend to show that adult

monkeys are more resistant than immature animals of the same species, and that their resistance may be due to the presence of anti-viral substances in their serum.

It has been found possible to increase the susceptibility of monkeys by exposing them to large doses of X-rays (Amoss, Taylor, and Witherbee, 1919, A 25). Animals so treated developed typical poliomyelitis even though they were inoculated with sub-infective doses of virus. There was a marked reduction in the number of circulating lymphocytes in each of the X-rayed monkeys. The authors suggested that there might be a "definite relation between these cells and one factor of resistance in poliomyelitis."

**Contact Infection.** The natural insusceptibility of monkeys is also evidenced by the fact that contagion from one animal to another has never been demonstrated (Leiner and von Wiesner, Z 3; Harmon, Shaughnessy and Gordon, H 14). In one instance, Levaditi and Danulesco (1912, L 38; L 39; L 34) kept a monkey in a small cage, smeared with virus, for 18 days. On the twentieth day after the first contact with the virus, symptoms developed. These authors concluded, therefore, that the absence of contagion among monkeys in the same cage was not due to the non-receptivity of the animals to the virus, but to the fact that in intracerebrally inoculated monkeys, the virus was not so abundantly spread about through the secretions of the nose and throat. The frequency with which the virus has been demonstrated, however, in the nasopharyngeal mucosa of monkeys, even after intracerebral inoculation (see *Distribution of the Virus in the Body*), would cast doubt upon this conclusion.

### Clinical History

*Incubation Period.* Although subject to variations dependent upon the resistance of the individual animal used, the route of inoculation, the virulence, concentration, and dose of the virus, there is general agreement among experimental workers with regard to the average incubation period: 6 to 10 days, Leiner and von Wiesner (L 28, I); 9 to 82 days, Flexner and Lewis (F 47); 4 to 11 days, Leake (L 18); 7 to 10 days, Levaditi (L 34); 5 to 8 days, Aycock and Luther (A 49); 9½ days, Zappert (Z 2); 7 to 11 days, Harmon, Shaughnessy, and Gordon (H 14).

Frequently, a prolonged incubation period is taken as an indication of an attenuated or partially neutralized virus (see *Section on Active Immunization*). Harmon and his associates (1931, H 14), on the other hand, believe that the virulence of the virus is not an important factor



in such atypical results. They find no significant difference in the degree of paralysis or in the histological picture in monkeys inoculated with a presumably modified virus as compared with that in monkeys that have received a more concentrated dose.

The effect of single and multiple lethal doses has recently been tested by Brodie (1932, B 31). "In a series of thirty-nine monkeys, each of which received anything from one to eighty M.L.D.'s of tissue containing virus, the incubation period, the onset of first paralysis, and the interval from the first onset of paralysis to complete paralysis of all limbs, are much the same in all cases." The average incubation period for twenty-six monkeys, each of which received one M.L.D. of virus was 8.3 days; for nine animals each of which received two to eight M.L.D.'s, it was 7.1 days; and for four, each of which received twenty to eighty M.L.D.'s, it was 7.5 days.

*Symptomatology.* "There is no experimental disease which so clearly reflects in its . . . clinical aspects the human analogue as does experimental poliomyelitis" (Amoss, A 18). The following brief account of the symptoms most frequently observed has been given by Harmon, Shaughnessy, and Gordon (1931, H 13):

"Preceding actual flaccid paralysis, which is, of course, the most striking manifestation of successful infection of the monkey with the filterable virus of poliomyelitis, there is a definite prodromal stage, described by a number of authors (Flexner and Lewis, F 47; Leiner and von Wiesner, L 28, I; Römer, R 24, R 23), and considered analogous to the preparalytic stage in the human disease. Immediately after intracerebral inoculation with a potent untreated virus, the monkey shows no symptoms save the effects of the anesthetic and the operation, and these usually disappear in less than an hour. Five to eight days after inoculation (one to three days before the onset of paralysis), the prodromal period occurs. The animal becomes either passive or restless. Then follows a period of excitement accompanied by frequent hoarse cries and ruffling of the fur, these signs being especially conspicuous when the animal is stimulated. Tremors, varying from a fine generalized tremor to coarse intention tremors, are an almost invariable accompaniment. Finally flaccid paralysis appears, the date of its onset in relation to prodromal symptoms depending upon the strain of virus used. With the virus of moderate potency, originally obtained from Aycock and used in most of our experiments, we have observed a consistent and well-defined prodromal period occurring from 24 to 48 hours, and in rare instances from four to five days, before the onset of paralysis. With the more potent virus obtained recently from Rhoads (1930, R 9)

prodromal symptoms have, as a rule, been observed only on the day immediately preceding paralysis. With the moderately potent Aycock virus the extension of paralysis, from its first appearance to the stage of total paraplegia, requires from 24 to 48 hours, while with the Rhoads strain less than 24 hours (sometimes 10 or 12 hours) suffice for the change from earliest prodromal symptoms to an almost total skeletal palsy."

As has been brought out by the above authors, it was formerly believed that there was no characteristic change in temperature during the prodromal period (Leiner and von Wiesner, L 28, I; Flexner and Lewis, F 47; Römer, R 25). Within the past few years, however, several groups of workers have demonstrated a regular elevation of temperature during this interval, so that it is now possible to determine with some accuracy the onset of the preparalytic stage in monkeys. Without making any comment, Hurst (1929, H 39) mentioned a rise in temperature in the protocols of a series of experiments. Ionesco-Mihaiesti, Tupa, Wisner and Mesrobianu (1929, I 3), however, pointed out that, in their monkeys, they were able to demonstrate that the temperature, though more or less regular before inoculation and during the incubation period, showed at a given moment an abrupt rise corresponding to the fever that marks the onset of human poliomyelitis. This elevation in temperature was observed 24 to 48 hours before the onset of paralysis and was accompanied by such symptoms as restlessness, weakness, and tremor. In normal monkeys the temperature seldom exceeded 39°C.; the preparalytic fever, however, frequently rose to 41°C. and sometimes to 41.5°C.

Early in 1930, Harmon, Shaughnessy, and Gordon (H 12) stated that they had noted a definite preparalytic elevation in temperature for 1 to 3 days before the onset of paralysis. Their complete report was published later (H 13) and was based on a large number of observations of the rectal temperatures of inoculated monkeys and of normal monkeys before inoculation. After inoculation, readings were taken both on monkeys that developed the typical disease and on others that failed to become paralyzed. It was found that a "marked rise in temperature of one degree to three degrees Fahrenheit always preceded actual paralysis, in most instances by three or four days, sometimes by one, two or five days." With the onset of paralysis, there was a drop to about normal (103.2°F. was determined to be the median normal temperature), and with complete paralysis, the temperature became subnormal, in some instances as low as 92°F. There were two types of



temperature curve. In one, the temperature was normal until the preparalytic rise and then remained high, though with slight fluctuations, until paralysis developed. In the other, the initial rise was followed by a drop, but a second elevation preceded the onset of paralysis, thus corresponding to the "dromedary type" sometimes referred to in the human disease. This curve was observed in 14 or 25.9 per cent of the 54 typical cases in these experiments.

A preparalytic rise in temperature, 1 to 3 days before the onset of the symptoms usually recognized, has also been described by Kramer, Hendrie, and Aycock (1930, K 26). Two "characteristic" temperature curves are illustrated by Demme (1930, D 10); in each there was a slight fall in temperature after the inoculation, with a rise above normal 2 to 4 days before the appearance of paralysis, and a sharp fall shortly before death. Daily temperature determinations have been employed, too, by Howitt (1932, H 36) as an aid in making an early diagnosis of the experimental disease.

## Types

The classification of the types presented by the human disease is discussed in the *Chapter on Symptomatology*. Brief reference only will be made here to the common forms observed in the experimental disease with some additional discussion of the more unusual ones.

*Spinal, Bulbar, and Cerebral Types.* In monkeys, as in man, the spinal type occurs most frequently; and, in spite of the fact that inoculations are so often made intracerebrally, the lower extremities are usually the first to be affected (see discussion under *Pathology*), although the descending form may occur; in some instances, the spread may be in both directions (Flexner and Lewis, 1910, F 47). The bulbar type, with involvement of the cranial nerve nuclei, is not infrequent (Leiner and von Wiesner, L 28, I; Römer, R 25). Instances of the cerebral type have also been described; in fact, the pathological evidence for the existence of this type is based on the findings in the experimental disease rather than on human autopsy reports (see discussion in the *Chapter on Symptomatology*). A "marantic" form was described by Leiner and von Wiesner (1910, L 28, II; Z 3) in which death occurred after a varying interval of weakness, although no paralysis could be demonstrated; Flexner and Lewis (1910, F 47) mention similar cases; both groups of workers found typical central nervous system lesions. These cases were not identical, Leiner and von Wiesner concluded, with the human abortive cases described by Wickman.

*Abortive Type.* Not infrequently reference is made in the literature to an "abortive type" of experimental poliomyelitis (Flexner and Lewis, 1910, F 47; Müller, 1911, M 53; Römer, 1913, R 25; Harmon, Shaughnessy and Gordon, 1931, H 14; Flexner, 1931, F 20). As with the human disease, the term has a different meaning, apparently, to different authors. In the *Chapter on Symptomatology*, abortive cases of the human disease are described as those in which the central nervous system is not involved while the nonparalytic type includes those cases with definite involvement of the nervous system but without evidence of paralysis.

The criterion for an abortive case adopted by Harmon, Shaughnessy, and Gordon (H 14) is "one resembling paralytic poliomyelitis in incubation period, preparalytic symptoms and changes in spinal fluid or in body temperature and blood, but without paralysis." By this standard, only 10 instances of abortive infections were observed following 555 intracerebral inoculations in 350 monkeys.

*Relapsing Cases.* The presence of both active and chronic lesions at the same time in the cord of a monkey that died in the chronic stage on the twenty-ninth day after inoculation was taken by Levaditi and Stanesco (1910, L 52) as an indication of the occurrence of the relapsing form of the disease. Römer (1913, R 25) mentions as a curiosity an instance of a definite relapse; a monkey that became paralyzed 12 days after inoculation showed distinct improvement 8 days later; a month after the inoculation, sudden weakness developed, followed by complete paralysis and death.

Two cases with an extremely long interval, in one 33 and in the other 51 days, between the intracerebral inoculation and the onset of paralysis have been described by Harmon, Shaughnessy and Gordon (1931, M 14). In both there occurred, at an intermediate period, nonparalytic symptoms and alterations in temperature and in spinal fluid. The authors believe that this constituted a nonparalytic attack and that, during convalescence, there was a relapse with definite paralysis. Both the abortive and relapsing cases, as well as the "missed infections" previously mentioned were considered by these authors the "result of differences in susceptibility in individual monkeys, rather than due to mild infection from an attenuated virus."

The question of second attacks is taken up in the *Chapter on Resistance and Immunity*; relapses and second attacks in the human disease are discussed in the *Chapter on Symptomatology*.



## Laboratory Findings

### Spinal Fluid

*Cytology and Protein Content.* Cell counts and globulin determinations in the spinal fluid have received less consideration in the experimental than in the human disease. Gay and Lucas (1910, G 5) reported an increase in cells, especially during the prodromal and early acute stages. Although poliomyelitis cells were often present, in some cases as high as 60 per cent, large mononuclears or lymphocytes usually predominated. A fibrin clot was noted at times but this disappeared early in the acute stage.

An excess of protein and a large increase in cells, partly polymorphonuclear and partly mononuclear in type were noted also by Flexner and Lewis (1910, F 44) and by Flexner and Clark (1911, F 31). The increase in the number of white cells was observed as early as 48 to 72 hours after an intracerebral inoculation; small cells with polyform nuclei predominated at first but after 72 hours, a large number of mononuclears had appeared.

More recently, the cellular changes in the spinal fluid of monkeys with experimental poliomyelitis have been studied with renewed interest. A rise in the cell count, 1 to 3 days before the onset of paralysis, was observed by Demme (1930, D 10) and regarded as significant for early diagnosis. Pleocytosis appeared very early in monkeys inoculated into the peripheral nerves, especially when the injection was made into the facial nerve; but the incubation period by this route was unusually short (3 days for the facial nerve, 5 days for the sciatic). Lymphocytes predominated; at most one-third of the total number were polymorphonuclear leucocytes.

Harmon, Shaughnessy and Gordon (1931, H 13) have been the first, however, to study the relationship between preparalytic changes in the spinal fluid and preparalytic temperature changes; it was found that, with few exceptions, the elevation of temperature definitely preceded the spinal fluid alterations by 1 or 2 days; in 6 monkeys, the two changes occurred simultaneously. Examination of 115 samples of normal monkey fluids showed variations in the cell count from 16 to 132 per cubic millimeter. A fluid, therefore, was not considered abnormal unless there were 150 or more cells per cubic millimeter, or 100 to 150 with a positive Ross-Jones test for globulin.

Spinal fluids were obtained at different intervals from 54 monkeys that developed paralysis while under observation. On 18 of these, 2

or more punctures were made during the 2 to 5 day preparalytic febrile period. On the day of the onset of paralysis, the fluid was found to be under increased pressure and to vary from a crystal clear to a "ground-glass" appearance, with a positive globulin; the cell count of the 17 fluids examined on this day varied from 253 to 1881; the higher counts occurred usually when paralysis was advancing rapidly; a differential examination was made in only 6 instances and, in these, all the cells proved to be monocytes. Fluids obtained on the second, third and fourth days of paralysis differed little from those obtained on the first day.

No variations from normal were observed in spinal fluids withdrawn 96 hours before paralysis; at 72 hours about half of those examined showed definite changes; and at 48 hours, most of the fluids from monkeys that later became paralyzed were pathological in character.

Although most of the above workers have reported a predominance of cells of the monocytic series, Brodie (1932, B 31) has found that a larger proportion of polymorphonuclear leucocytes usually occurs in the preparalytic stage, with mononuclear cells predominating after the onset of paralysis.

*Colloidal Gold Test.* Only one study of the colloidal gold reaction on spinal fluids in experimental poliomyelitis has been published. From an examination of the spinal fluids from 10 normal *rhesus* monkeys, Jungeblut and Khorazo (1930, J 25) found that a slight reaction, never over 1+, extended over the first 3 tubes or even over as many as 5 or 6 tubes. A total of 61 specimens was obtained from 44 monkeys at different stages of the experimental disease. From 75 per cent of the samples taken at the onset of symptoms a colloidal gold curve was obtained that showed a definite elevation in the second, third or middle of the series of dilutions and thus corresponded to the luetic zone curve, although the reactions were less marked than those obtained in syphilis. Later in the disease, the curve showed a shift forward or flattened out to one resembling that observed in the normal fluids. Thus any significant changes were limited to the earliest stages of the infection. The results described are not unlike those reported for human poliomyelitic spinal fluids (see *Chapter on Symptomatology*).

### Clinical Examination of the Blood

*Cytology.* Although the majority of workers have reported a leucocytosis in human poliomyelitis, it may be said that there is no characteristic blood picture by which a diagnosis can be established



(see *Chapter on Symptomatology*). The question of differential diagnosis, however, does not enter into the study of the experimental disease; if it could be established that any variation from normal occurs regularly, it would be helpful, in conjunction with other objective findings, in making an early diagnosis. According to Gay and Lucas (1910, G 5) a leucopenia occurred early in the acute stages of the disease, with a relative increase in eosinophils and lymphocytes. On the other hand, Broughton-Alcock (1912, B 33) made daily blood counts on 6 inoculated monkeys and found that the variations which occurred showed no regularity and appeared also in the 4 controls.

A much larger series was described later by Taylor (1919, T 4). In addition to 121 counts on 40 normal monkeys, numerous counts were made on 30 inoculated monkeys in various stages of the disease; as not all of the animals could be observed during all the stages, averages of counts in several monkeys were used for comparison. After inoculation, the relative and actual numbers of lymphocytes were diminished, with a "lymphocytic crisis" at the onset of symptoms; while this curve continued downward, the polymorphonuclear neutrophilic leucocytes increased both relatively and actually. During the stage of prostration, the lymphocytes were still further diminished and the polymorphonuclears returned to almost normal. The lymphocytes did not return to normal until several weeks after the height of paralysis. Taylor's findings with regard to the increase in neutrophilic leucocytes in the preparalytic stage have recently been confirmed by Harmon, Shaughnessy and Gordon (1931, H 13) but not those with regard to the changes in the lymphocytic curve. They comment that Taylor determined the normal blood picture by an average of calculations made on several animals instead of establishing an individual standard for each monkey. Harmon and his associates had found that different animals showed considerable variation in blood counts, but that a standard could readily be obtained for an individual animal. They note also that Taylor did not make daily blood counts and thus may have observed only the transient increase in the polymorphonuclear cells that follows an intracerebral inoculation (not all of Taylor's monkeys, however, were inoculated intracerebrally).

By making daily blood counts on 26 *rhesus* monkeys, both before and after inoculation, Harmon, Shaughnessy and Gordon (H 13) determined the normal blood picture and the variations which occurred after inoculation, during the preparalytic febrile period, and during and subsequent to the stage of paralysis. The erythrocyte count was not

affected during the course of the disease and averaged slightly over 6,000,000 cells per cubic millimeter as determined by observations on 17 monkey's before and after inoculation. There was also no constant variation in the total number of leucocytes; the average leucocyte count of 24 normal animals was 19,560 per cubic millimeter; of the 26 inoculated monkeys, 12 did not become paralyzed and showed an average count of 20,710; 14 developed paralysis and the average counts of this number, made at different stages, showed only unimportant changes from the above; in a few individual instances, however, a preparalytic leucocytosis was observed.

Differential counts, however, gave a different picture. Inoculation was followed by a definite, though transient, increase in the polymorphonuclear leucocytes, but the number of lymphocytes remained unchanged. After returning to the normal level, the number of neutrophils varied little until the onset of the preparalytic stage as indicated by an elevation in temperature, when a second and more prolonged increase took place. At this time, there was a drop in lymphocytes, often sufficiently great to counterbalance the increase in polymorphonuclear cells so that the total white count, while correct, remained approximately the same. In some instances, however, the increase in neutrophilic leucocytes was sufficiently great to produce an actual increase in the total number of cells. In 75 per cent of the cases, the number of polymorphonuclear cells rose coincidently with the preparalytic elevation of temperature; in the other cases, it occurred 1 or 2 days later. As paralysis extended and the monkey became prostrate, there was a marked drop in both lymphocytes and polymorphonuclear neutrophilic leucocytes, with a consequent leucopenia.

At no time was any modification observed in the normal numbers of eosinophilic or basophilic leucocytes or of transitional cells.

*Sedimentation Velocity.* Determination of the sedimentation rate of the red blood corpuscles in citrated blood is a test that has heretofore had only a limited clinical application in any disease. Two reports have, however, been published on the speed of erythrocyte sedimentation in experimental poliomyelitis and three on the rate in the human disease.

Following the procedure of Linzenmeier, Kagan (1929, K 2) determined the sedimentation time in a group of 14 normal monkeys and compared it with the rate in a group of 5 monkeys with tuberculosis and with another of 20 monkeys sick with poliomyelitis. In this last group, although the stage of the disease is not specified, it may be



inferred that the animals were prostrate with extending paralysis. By the method used the sedimentation time of this group was considerably shorter (2 hours and 39 minutes) than that for healthy monkeys (19 hours and 32 minutes) although it exceeded the time for animals with tuberculosis (1 hour and 20 minutes). In the 3 instances, in which the test was repeated several months after the acute symptoms of poliomyelitis had disappeared, the sedimentation time was normal.

The results obtained by Harmon, Shaughnessy and Gordon (1931, H 13) are not readily compared with those given above as a different technic (that described by Fåhræus) was used. The median normal rate in *rhesus* monkeys by this method (59 observations) was found to be 5 mm. per hour. Daily determinations were made upon 12 inoculated monkeys, 6 of which developed typical paralysis. During the incubation period and in the preparalytic stage, the sedimentation speed was remarkably constant; acceleration did not take place (with but 1 exception) until at least 24 hours after the onset of paralysis, when the monkey was prostrate.

The sedimentation velocity in the human disease has been discussed by Huss (1931, H 45), Lichtenstein (1931, L 58), and by Zollikofer and Custer (1932, Z 9).

### Experimental Studies in Therapy

**Chemotherapy.** A few attempts have been made to prevent the development of, or to influence the course of, the experimental disease with pharmacological preparations of various classes, but usually with little or no effect. Arsacetin, arsenophenol, glycin and ethylhydrocuprein (Landsteiner and Levaditi, cited by Römer, R 25, and by Thomsen, T 12), trypan red (Römer, R 25), chloramine-T and an oily solution of dichloramine-T as a nasal wash or spray (Flexner and Amoss, F 28), silversalvarsan, neosalvarsan, tryparsamide, colloidal bismuth, bismuth potassium tartrate, triphal (an organic gold compound), methylene blue silver, metaphen, plasmochin, Bayer 205 (Germanin) (Jungeblut, J 16), all have given negative results in the experiments reported. Potassium permanganate and iodine applied to the nasal mucosa prevented infection in a few instances but not regularly (Levaditi and Danulesco, 1912, L 40).

A certain inhibiting effect was obtained with hexamethylenamin (urotropin) (Flexner and Clark, 1911, F 31). When given by mouth in large doses, this substance appears soon after in the spinal fluid. If hexamethylenamin was already present in the fluid, when virus was

injected intracerebrally, and if the drug was then given daily by mouth, the incubation period was in some instances prolonged from 6 to 8 to 24 days, and paralysis was prevented.

Attempts to block infection by way of the nares with hexamethylenamin were, however, unsuccessful (Flexner and Amoss, 1920, F 28). Normal horse serum was first given intraspinally. Then a cotton tampon with virus was placed in the nostril. The drug was given by stomach tube twice a day for 6 days. The monkey developed poliomyelitis.

When administered repeatedly during the incubation period, Jungeblut (1930, J 16) observed that two antimony compounds (antimony potassium tartrate and neostibosan, an organic compound) and chaulmoogra oil ester had a certain prophylactic effect. Of 11 antimony-treated monkeys, 5 developed an infection as severe as that of the controls, but 3 showed no symptoms, 1 had a slight transitory paresis of one arm only, and 2 developed a much delayed paralysis. Two of the 4 animals that received chaulmoogra oil remained well and the other 2 developed only a partial paralysis. Of 5 monkeys treated with hexyl-resorcinol, 1 escaped infection, 1 developed an "abortive" case, and 3 died; the intraspinal route was thought to be the most effective for this drug. Two monkeys, treated with mercurochrome, developed only a partial paralysis and recovered almost completely. In the controls, the morbidity was 100 per cent and the mortality was very high. Trypan blue, administered intravenously also gave promising results in later tests (personal communication).

**The Action of Subdural Injections of Epinephrin.** The effect of epinephrin in contracting actively hyperemic vessels with a resultant reduction in local edema suggested that it might prove of value in the treatment of poliomyelitis (Clark, 1912, C 12). The action of subdural injections of epinephrin on monkeys paralyzed as a result of an intracerebral inoculation of virus was studied; the animals all had an extensive paralysis or were moribund; in no case was life actually saved, but, in some instances, it was greatly prolonged and the symptoms were definitely ameliorated; there was, in general, improvement in the muscular tone of the paralyzed muscles and in the respiratory movements. When employed early in the course of the paralysis, the progress of the disease was not arrested; the value lay in the prolongation of the life of moribund monkeys for several hours or even for several days.

**Artificial Fever.** The therapeutic effect of high temperatures artificially induced, on the course of experimental poliomyelitis has recently been described by Jungeblut and Kopeloff (1931, J 26). In



view of the reported success of such treatment in neurosyphilis and other disorders and of the low heat resistance of the poliomyelitis virus (see under *Properties of the Virus*), it was felt that there was a rational basis for such an experiment. Three methods of inducing fever were tried: the injection of foreign protein (milk), infection with *Trypanosoma equiperdum* and with *Spirochaeta recurrentis*, and radiothermy. By intramuscular injections of boiled milk during the first 4 days of the incubation period a temperature of 104° to 105°F. was maintained, but the 1 monkey so treated developed poliomyelitis 4 days before the control. Four monkeys were infected with trypanosomes and inoculated intracerebrally on the same day with virus; a temperature of 104° to 106°F. resulted from the infection; symptoms, ending in complete paralysis, developed at the same time as in the 2 controls. The same result was obtained with the monkey inoculated with the spirochete of relapsing fever; although no spirochetes could be demonstrated in the circulation, the temperature rose to 105° and 106°F. Three animals were treated by radiothermy; 1 died, apparently as a result of the first treatment during which a temperature of 108° to 110°F. was maintained for an hour; thereafter, the temperature was not allowed to exceed 108°, and averaged 106° to 107°F. for an hour and a half; 1 monkey received 6 such treatments and another, 4; there was no important difference in the course of the disease in the 2 treated animals and in the control. Two convalescent monkeys were also treated by radiothermy; they showed evidence of a greatly decreased resistance to the effect of short radio waves; 1 died after 10 minutes exposure, although a normal monkey showed a temperature elevation of only a fraction of a degree when treated for the same period with the same amperage and voltage; the other convalescent had a rectal temperature of 107.5°F. after similar treatment for 7 minutes and was found dead the next day. The authors suggested that poliomyelitis may cause a disturbance of the heat-regulating centers of the brain.

**Effect of Roentgen Rays.** The use of roentgen rays has frequently been advocated in the treatment of paralyses occurring in the course of the human disease. Römer (citing Levaditi, R 25) referred to the fact that radium and X-ray had been ineffective either for the prevention or cure of the experimental disease.

Exposure of monkeys to large doses of X-rays has been found to result in a lowered resistance to even a weak poliomyelitic virus (Amoss, Taylor and Witherbee, 1919, A 25). Recently a study has been made

of the effect of therapeutic doses on monkeys suffering with the experimental disease (Lenz and Jungeblut, 1932, L 31). Seven animals in various stages of paralysis received either one or repeated X-ray treatments, directed over the areas corresponding to the cervical and lumbar enlargements of the spinal cord; 2 were found dead on the morning following the first treatment and 2 others on the second day. In the 6 animals that died, paralysis had progressed in the usual manner; the histological lesions were, perhaps, more intense than in the controls. One monkey survived and appeared to improve rapidly, but the authors feel that this may have been due to chance rather than to the effect of treatment. The effect of X-ray during the incubation period was tested in 2 instances; two treatments were given, one over the site of inoculation (intracerebral) on the day of injection, and one 3 days later over the cervical and lumbar cord. Both monkeys developed the typical disease as did the control. (*Serum treatment of the Experimental Disease* is discussed in the *Chapter on Resistance and Immunity*.)

### **The Transmission of Poliomyelitis to Animals Other than Monkeys**

Experimental work in poliomyelitis would be greatly facilitated if the human infection could be successfully reproduced in some animal other than the monkey. As we have seen the first attempts at the transmission of the disease were made with rabbits. With few exceptions, the results with other laboratory or domestic animals have been avowedly negative. Some controversy, however, has arisen with regard to the susceptibility of the rabbit. As the literature on the transmissibility of the virus to rabbits and other animals has recently been reviewed by Harmon, Shaughnessy, and Gordon (1930, H 12), their discussion may be quoted here with only a few additions.

**Rabbits.** "At the time of the 1909 epidemic in Germany, successful transfers of poliomyelitis to rabbits were reported by Krause and Meinicke (1909, K 33; 1910, K 34), Meinicke (1910, M 34, M 35), Lentz and Huntemüller (L 30), Bonhoff (1910, B 20, B 21), Beneke (1910, B 10), and Dahm (1909, D 1). Krause and Meinicke produced death with 'symptoms which pointed to a lesion of the spinal cord' and found pathological alterations such as congestion of the blood vessels, hemorrhages and cell degenerations in the grey matter, particularly of the brain. Bonhoff and Beneke and Römer inoculated rabbits with the same pathological materials, taken from human cases, at the same time and in conjunction with one another, Bonhoff with negative results,



Benecke with results which he considered positive (death in three rabbits, only one of which was paralyzed). Römer (R 21) directly refuted the work of Krause and Meinicke with a clear-cut series of experiments, in which rabbits and monkeys were inoculated with the same material simultaneously, the former remaining without symptoms, the latter becoming typically paralyzed when brain and spinal cord were employed. Römer and Joseph (R 27) and Römer (R 24; R 25) after further experiments pointed out, in the reports made by Krause and Meinicke and others of successful rabbit transmission of poliomyelitis, a number of misinterpretations and fallacies, such as the lack of similarity in the histopathological picture, lack of adequate inquiry into other possible causes of death, lack of flaccid paralysis and use of blood and lumbar puncture fluid as inoculum. Römer discussed also the greater efficacy with rabbits of the intraperitoneal and intravenous methods of introducing the virus as compared with the intracerebral method so uniformly effective in monkeys, and the frequent prostration of uninoculated rabbits with symptoms identical with those alleged to be indications of 'rabbit poliomyelitis.'

"Other competent investigators who demonstrated, at about the time of the controversy between Römer and Krause and Meinicke, the uniform unsusceptibility of the rabbit to the materials that consistently produced paralysis in the monkey, were Flexner and Lewis (1910, F 47), Leiner and von Wiesner (1909, L 28, I), Landsteiner and Levaditi (1909, L 5; 1910, L 44), and Kraus (1910, K 27, K 28). The instance in Landsteiner and Levaditi's experiments (L 44) of a single rabbit, out of a number inoculated intracerebrally with monkey passage virus, that died 24 days later without showing signs of paralysis, should be noted. Histological examination of the spinal cord and brain showed focal infiltrations in the cord similar to those of human and monkey poliomyelitis. The most characteristic change (perivascular infiltration), however, was lacking, and the authors concluded that this was some other affection of the central nervous system, but 'similar' to poliomyelitis.

"Belief in the susceptibility of rabbits has been kept alive especially by the experiments of Marks (1911, M 21) at the Rockefeller Institute, who asserted that some, but not all, rabbits were susceptible, following intravenous and intraperitoneal introduction of monkey passage virus, and that he was able to propagate the activity through seven generations. Histological examination 'revealed nothing definite.' This investigator thought he determined the presence of the poliomyelitis virus in

rabbit brains of the second, fourth and sixth rabbit passages, because intracerebral reinoculation into monkeys produced apparently characteristic clinical and anatomical pictures of the disease.

“A few confirmatory investigations have been published. Rosenau and Havens (1916, R 35) were able to pass the virus through eight generations in rabbits, finding that out of 54 rabbits inoculated 22 (or 40 per cent) succumbed. They state that young rabbits must be employed. Several methods of inoculation were successful—intracerebral, intravenous, intravascular and intranasal. The pathological findings of these authors ‘although definite and constant throughout the series, lack the distinguishing features of the pathological picture of poliomyelitis in man and in the monkey;’ perivascular infiltration, the most typical lesion, was absent. Two factors—the omission of any attempt to retransfer the infection to monkeys and the presence of a highly variable incubation period (2 to 41 days)—detract considerably from the strength of the argument that the condition produced was actually rabbit poliomyelitis. Recently a group of Italian authors has presented work, which, they consider, proves that the rabbit is susceptible to poliomyelitis; their experiments, however, are all based on the use of cerebrospinal fluid from human cases, which, as mentioned above, has been convincingly proved to be devoid of virus (Sindoni and Misasi, Leone and Gerbrasi, and quoted by Jemma 1926, J 5).”

Against these alleged positive results, failures to induce the disease in rabbits have been reported by Amoss (1918, A 13), Stimson (1918, S 60), Mathers (1917, M 24), Nevin and Bittman (1924, N 17) and Fairbrother (1929, F 3). “Amoss, in carrying out experiments to determine the limits of viability of the poliomyelitis virus in the brain of the rabbit, states: ‘The virus of poliomyelitis is unadapted to the rabbit, and neither induces lesions nor survives long in the central nervous organs of that animal.’ Using intracerebral monkey inoculations as the indicator, he found that the maximum survival time in the rabbit was four days. Stimson observed death in rabbits inoculated intracerebrally, intraperitoneally and intravenously, and by a combination of these methods, with material from experimental monkey poliomyelitis. From the evidence of a varying incubation time, from failure of rabbit material to immunize monkeys against virus inoculations, and from histological studies, he concluded that the deaths had not been due to virus inoculation. Mathers injected filtrates from brains and cords of poliomyelitis patients intracerebrally, intraperitoneally and intravenously into rabbits without the animals showing any evi-



dence of infection. Nevin and Bittman, using monkey passage virus by all the routes previously described, failed to obtain any specific effects in rabbits, save in two instances out of 36, where actual flaccid paralysis was observed. More than half the animals used were dead within a week or two after the inoculations. Five serial passages were made; monkeys were inoculated intracerebrally with brain and cord emulsion from the fourth passage without effect. Histological examinations were made of the brain and cord of eleven rabbits, eight of which (including the two that had had flaccid paralysis) showed no changes either in the meninges or brain substance. Three rabbits of the first passage in which no symptoms developed showed a 'slight amount of neurophagocytosis of ganglion cells and some cellular degeneration, with no evidence of perivascular infiltration.' "

Positive results have also been described by Krauspe (1928, K 35). In 3 out of 5 experiments, flaccid paralysis followed by death developed in rabbits inoculated (route not stated) with human virus-containing cord substance. The histological findings (perivascular infiltration, proliferation of neuroglia cells, and degeneration of ganglion cells) were considered similar to those characteristic of the human and the experimental disease in monkeys. But the author admitted that such a picture might sometimes be found in spontaneous rabbit encephalitis, and that 2 rabbits from the other two sets of experiments showed similar, though less marked, histological changes. In 2 instances, however, monkeys inoculated with brains of the affected rabbits developed paralysis after an 8 day incubation period with typical alterations in the medulla. Thus Krauspe concluded that he was dealing with a true rabbit poliomyelitis as there is no evidence that spontaneous rabbit encephalitis is transferable to monkeys.

On the other hand, three groups of observers (Fairbrother, Harmon, Shaughnessy and Gordon, and Thompson) have recently re-investigated this question and have found no support for the belief that poliomyelitis is transmissible to rabbits. It may be mentioned here that Tsen (1918, T 19) was also unable to produce typical lesions in rabbits by the injection of poliomyelitis virus.

Fairbrother (1929, F 3) described three sets of experiments. In the first, 24 rabbits were inoculated with a monkey strain of virus, intracerebrally, intravenously, or intraperitoneally, or in combination. Only 6 animals died; these had all been inoculated intracerebrally; 4 died within 24 hours apparently as a result of the operation. Only 1 of the other 2 was autopsied; death had occurred suddenly after 7

days; histological examination was negative. In the second experiment, 6 rabbits were inoculated intracerebrally or by the combined intracerebral and intraperitoneal routes, with human virus. These animals all survived. In the third experiment, an attempt was made to accommodate the virus to rabbits by injecting an emulsion intracerebrally, removing the region of the brain around the site of inoculation 24 hours later, and reinjecting intracerebrally into other rabbits. No evidence of poliomyelitis was obtained. Three of the 4 animals of this group that died proved to have a pasteurella infection. Rabbits, 4 to 6 weeks old, had been used in all of these experiments. Fairbrother concluded that young rabbits do not "react even in a modified form to the virus of poliomyelitis."

The most exhaustive study of the effect upon rabbits of inoculation with poliomyelitis virus is that reported by Harmon, Shaughnessy, and Gordon (1930, H 12). Two series of controls were carried; in the first, the animals were inoculated with either normal monkey brain or normal rabbit brain; in the second, they were uninoculated. Young animals, 4 to 8 weeks old, were used throughout. Four sets of experiments were described; in the first, inoculations were made with poliomyelitis virus derived from monkeys; in the second, nervous tissue from rabbits previously inoculated with monkey virus was used; and in the third and fourth, nervous tissue from rabbits of successive virus passages. The authors' summary and conclusions are given below.

### Summary

"Inoculation of poliomyelitis virus, of potency proven by tests upon *Macacus rhesus* monkeys, into young rabbits by the combined intraperitoneal-intracerebral method was followed by death in many of the rabbits with symptoms of prostration, convulsions and transient motor pareses. Similar symptoms and death occurred in rabbits inoculated with brain and cord from normal rabbits and normal monkeys, also in rabbits that were never inoculated.

"When an emulsion of brain and cord removed from rabbits dead following inoculation of monkey passage virus was introduced into other rabbits, death followed in the second, third and fourth series of rabbits, thus simulating virus transfer from one generation to another. It was shown, however, that no poliomyelitis virus was involved in these transfers because rabbit brains of three different passages in five instances failed to induce poliomyelitis in monkeys, although inoculated intraperitoneally-intracerebrally in large quantities.



"The mortality rates in virus-inoculated and in normal-brain-inoculated rabbits were about the same.

"The correspondence in symptoms and mortality rates for the two groups of inoculated rabbits (one receiving supposed virus material, the other receiving normal brain) indicated that some other factor than the transmission of poliomyelitic virus from rabbit to rabbit was responsible for the symptoms and deaths. This other factor was in all probability the miscellaneous intercurrent infections and infestations, since pathological examination of both groups of inoculated rabbits and also of rabbits never inoculated showed demonstrable gross lesions in a large proportion.

"A comprehensive series of weights, temperatures, red blood cell counts and total white cell counts showed no essential difference between rabbits inoculated with virulent poliomyelitis virus and those inoculated with normal-rabbit and normal-monkey brain and cord. Apparently such observations were of no use as an indication of the presence of poliomyelitic virus in the rabbit.

"Lesions suggestive of poliomyelitis were found in the central nervous system of 4 of the 41 rabbits which had been inoculated with monkey virus. The most suggestive lesions were observed in the spinal cord of a rabbit which had shown no motor symptoms during five weeks following virus inoculation. This rabbit was the only one, in any series, in which perivascular infiltrations were found. In a series of uninoculated rabbits, dead spontaneously or chloroformed when apparently in a normal state of motor coördination, brain lesions occurred in substantially the same proportion of rabbits as in the inoculated series. There was, in all the series, a relative absence of neurophagocytosis and perivascular infiltrations, the most characteristic of the lesions of poliomyelitis as it is known in man and in monkey.

### Conclusions

"1. In attempts to transfer poliomyelitis to a series of young rabbits with monkey passage virus of proven pathogenicity, no evidence was obtained that rabbits are susceptible to the disease.

"2. The occasional death of inoculated rabbits, sometimes with suggestive motor symptoms, is best explained upon the ground of the exquisite susceptibility of young rabbits to intercurrent infections.

"3. Convulsive seizures and other motor symptoms, as well as certain cellular changes in the central nervous system of rabbits inoculated with poliomyelitis, are non-specific in nature, identical symptoms and

cellular infiltrations being observed both in rabbits inoculated with normal rabbit brain and normal monkey brain, and in uninoculated young rabbits."

Attempts to adapt the virus of poliomyelitis to rabbits by various methods have also resulted in failure (Thompson, 1930, T 8). Testicular injection and brain injection after testicular passage was ineffective. In a few instances, suggestive symptoms developed in very young rabbits but these were observed also in nonspecifically treated and in uninoculated controls. A mixture of vaccine virus and poliomyelitis virus in similar injections and passages was also ineffective. Nor could the disease be transmitted to rabbits by repeated intraperitoneal and intradermal injections of the poliomyelitis virus alone or of mixtures of the poliomyelitis and vaccinia viruses. The administration of massive doses of concentrated virus by stomach tube together with meningeal irritation also failed to induce symptoms.

Very few references have been made in the literature to the presence or absence of neutralizing substances in the serum of rabbits inoculated with the poliomyelitis virus. Flexner (1910, F 11) stated that the rabbit did "not seem to yield such immunity principles." An attempt was made by Tsen (1918, T 20) to immunize rabbits by subcutaneous injections of virus but he was unable to obtain a serum with neutralizing properties. Thompson (1930, T 8) also found no evidence of neutralizing substances in the serum of rabbits that had received repeated intraperitoneal and intradermal injections of poliomyelitis virus or of poliomyelitis-vaccinia virus mixtures.

**Other Animals.** (Sheep, goats, calves, pigs, dogs, cats, pigeons, chickens, rats, mice, guinea pigs.) Experimental workers agree, almost unanimously, that the above mentioned animals are refractory to poliomyelitis. The review of the literature given by Harmon, Shaughnessy and Gordon (1930, H 12) is quoted here.

"Landsteiner and Popper (L 11), who were the first to accomplish experimental transfer of human poliomyelitis to monkeys, failed with the same virus emulsion to produce any effect upon guinea pigs and mice. Leiner and von Wiesner (L 28, I), who utilized young dogs, hens and pigeons, obtained uniformly negative results. Krause and Meinicke (K 33), in spite of the fact that they were enthusiastic champions of the susceptibility of rabbits, were not able successfully to inoculate mice, guinea pigs, pigeons or domestic fowls. Römer (R 21) in an early paper reported failure to infect either mice or guinea pigs, while later (R 22) a goat and a sheep were also found to be non-susceptible. Flex-



ner and Lewis (F 42; F 47) found that 'many guinea pigs, one lamb, two calves, three goats, three pigs, three sheep, six rats, six mice, six dogs, and four cats have had active virus introduced into their brain without causing any appreciable effect.' Mathers (1917, M 24) likewise was unable to infect guinea pigs. Stimson (1918, S 60), in an elaborate series of inoculation experiments with guinea pigs and rats, produced death regularly, but, as histological examinations failed to reveal lesions, he concluded that these animals did not react with recognizable poliomyelitis.

"In contrast to the results just reviewed stand the guinea pig experiments of Neustaedter (1913, N 13) and of Picard (1925, P 19). The former noted flaccid paralysis in two guinea pigs which occupied a cage beneath a virus-inoculated monkey. Spinal cord and nasal mucus removed from one of these animals and inoculated into two other guinea pigs resulted in death preceded by convulsive seizures. An intranasal tampon moistened with filtered monkey virus produced paralysis in a guinea pig on the second day after inoculation. Histological examination of the central nervous system revealed the perivascular infiltration with neurophagocytosis so typical of poliomyelitis in man and in the monkey. Picard reported a similar spontaneous induction of poliomyelitis in three guinea pigs kept in close proximity to infected monkeys. Experimental transfer from guinea pig to guinea pig by means of intracranial inoculation was successful. Creutzfeldt (1925, C 32) was able to demonstrate typical poliomyelitis-like alterations in the spinal cords of Picard's guinea pigs."

A few additional authors have reported negative or equivocal results. Guinea pigs and chickens were refractory, according to Lentz and Huntemüller (1910, L 30), although these workers believed that they had produced the disease in rabbits. Hassin (1917, H 15) refers to poliomyelitis as observed in sheep, which had received intracerebral or intraperitoneal injections of human virus mixed with spinal fluid cultures and also as observed in 1 passage animal. No adequate description is given of the symptomatology. The sheep were said to present less marked anatomical changes than monkeys; either the infiltrative or the degenerative type of alteration might prevail; but he admits that a definite or certain pathological diagnosis could not be made in any of the animals of his series (sheep or rabbits) by any means.

Although preliminary orientation experiments with mice, rats, and cats were negative, Krauspe (1928, K 35) expressed himself as not ready to give an opinion concerning the results with guinea pigs. Inocula-

tion with virus frequently induced a picture resembling poliomyelitis but without the typical histological findings.

In addition to their studies on the susceptibility of rabbits described above, Harmon Shaughnessy, and Gordon (1930, H 12) have reported the results of inoculation of young animals of 7 other mammalian species—dogs, cats, guinea pigs, mice, pigs, lambs, and calves. A double control series was used, as in the rabbit experiments; in one, the animals were inoculated with normal monkey brain, and in the other, they were not inoculated. Their summary and conclusions are given below.

### Summary

“Poliomyelitis virus whose potency was carefully controlled by parallel inoculations into rhesus monkeys was introduced in massive doses, both into the central nervous system and by other routes, into many representatives of a variety of species of mammalia.

“Of eleven dogs inoculated with poliomyelitis virus in three successive experiments, but two succumbed. At the same time, of seven dogs that were inoculated with normal monkey brain emulsion three succumbed. No symptoms were observed at any time in the animals that survived. Similar findings were obtained among uninoculated control animals. Postmortem examinations of the fatal cases showed bronchopneumonic changes in the lungs, while both in these animals and in many that showed no effects following inoculation, no alterations were found in a carefully conducted search through many levels of the central nervous system.

“Of twelve young cats inoculated with virus three succumbed, while among five control animals receiving normal monkey brain none succumbed. No symptoms were observed in animals that did not die. Gross pathological examination, confirmed by microscopic methods, showed that when death occurred it was due to acute respiratory disease. Microscopic observations, extended to many levels of the central nervous system both in cats dying from respiratory disease and in those killed following an uneventful five-week observation period, failed to demonstrate changes.

“Three diversified experiments with poliomyelitis virus on 25 guinea pigs resulted in the death of 13 of these animals. Among 15 controls receiving normal monkey brain, three succumbed. In a majority of instances, gross and microscopic pathological methods showed that death was due to acute respiratory disease. Careful search through many microscopic sections of the central nervous system failed to reveal changes that might be interpreted as those of poliomyelitis.



"Among 32 virus-inoculated white mice, 10 succumbed in the five-week observation period, while among 32 normal-monkey-brain-inoculated mice, 7 succumbed in a similar period. No symptoms suggestive of flaccid motor paralysis were observed in any of these animals. Gross pathological observations established the cause of death in a majority of instances as acute respiratory disease.

"Of four young pigs inoculated with massive doses of virus, none showed symptoms. Two young pigs receiving normal monkey brain showed no effects during the observation period.

"Two of four virus-inoculated lambs developed suggestive motor incoordination, but this symptom was shown to be the concomitant general prostration of pneumonia. No symptoms were observed in control animals. No alterations were found in the central nervous system of the affected animals.

"Two of three calves succumbed following virus inoculation, but no alterations could be demonstrated in a careful examination of the central nervous system.

### Conclusions

"Young dogs, young cats, guinea pigs, mice, young pigs, lambs and calves do not develop any condition recognizable as, or related to, poliomyelitis, following massive inoculation of virus of established pathogenicity for monkeys. Although a small proportion of inoculated animals succumb, death is due, in the main, to acute intercurrent respiratory disease."

### CHAPTER III

## RESISTANCE AND IMMUNITY

### MECHANISMS OF DEFENSE

The low case incidence of epidemic poliomyelitis has generally been taken to indicate that many persons are exposed to the virus without developing the disease (Kling and Levaditi, 1913, K 12; Müller, 1922, M 54; Aycock and Kramer, 1930, A 46), although it must be admitted that this inference is only an indirect one and not based on any direct experimental evidence. In view of the fact that the upper respiratory mucosa has been considered the main portal of entry of the virus (Flexner and Lewis, 1910, F 43; Levaditi and Landsteiner, L 47; see also under *Routes of Inoculation* and *Chapter on Pathology*), Flexner and his associates have discussed the mechanism which prevents its ready access to the central nervous system. In the first place, the virus may be destroyed before it infects or passes through the mucous membranes. Neutralizing substances have been shown to be present in the nasopharyngeal secretions of some persons though absent in others. They may be present on one occasion and absent at another, even in the same individual (Amoss and Taylor, 1917, A 24).

The normal nasal mucosa has also been considered an important factor in preventing infection of the central nervous system (Flexner and Amoss, 1920, F 28).

Even if these defense mechanisms fail, infection by the virus may not take place, if the meningeal-choroidal plexus complex is intact. Early in the course of experimental work, it had been found (Flexner and Amoss, 1914, F 21, F 22) that infection did not readily follow intravenous injection of the virus; passage of the virus from the blood into the spinal fluid required time; but the virus readily penetrated the cord and brain from the blood if an aseptic inflammation had first been set up in the choroidal plexus by intraspinal injection of sterile horse serum (see *Routes of Inoculation*).

It was later found that this complex was a factor in preventing infection by virus applied to the nasal mucous membranes or injected subcutaneously (Flexner and Amoss, 1917, F 24; Flexner, 1917, F 16). Moreover, it was not even necessary to use a foreign (horse) serum to



break down the meningeal protective mechanism, but an aseptic meningitis could be set up by the injection of an homologous (monkey) serum, of Ringer's or Locke's solutions, of Locke's solution plus 0.5 per cent gelatin, or even of sterile isotonic salt solution. In addition, although uncomplicated lumbar puncture, or the simple removal and return of the spinal fluid in the same monkey did not promote infection after intravenous inoculation, interchange of fluid from one monkey to another did so operate in some instances. Even injury to the blood vessels of the meninges as evidenced by a slight hemorrhage at the time of the lumbar puncture affected the result. Flexner concluded that "the intact meninges are a protection from nasal as from intravenous inoculation with the virus of poliomyelitis, as, conversely, the pathologically altered meninges are a cause of heightened susceptibility to the action of the virus present in either place."

The presence of immune bodies in the serum constitutes, presumably, an additional factor in the mechanism of defense. Recent studies would suggest that other nonspecific factors, such as endocrine balance, clinical types, blood groups, and the presence of neutralizing substances associated with universal biological phenomena, may play a more important part in the resistance to infection with the poliomyelitic virus than was formerly believed.

## IMMUNITY

### Immunity Following an Attack of the Disease

**Resistance to Re-infection.** Clinical and epidemiological observations had indicated that one attack of poliomyelitis usually conferred immunity. Flexner and Lewis (1910, F 47), Levaditi and Landsteiner (1910, L 44), Römer (1910, R 22, R 25), and Leiner and von Wiesner (1910, L 28, Z 3) confirmed these observations with experimental tests. Monkeys were found to be refractory to re-inoculation at periods varying from 8 days to 2 months (Flexner and Lewis) and from 2 to 99 days (Leiner and von Wiesner) after onset of paralysis. In one of the experiments described by Leiner and von Wiesner, a monkey was reinoculated 17 days after the onset of paralysis; 18 days later, acute symptoms again developed and the paralysis became more extensive. Although the possibility of a second attack was considered, it seemed more likely that in this case there had been a relapse.

Contrary to the general experience, Krauspe (1928, K 35) has reported that recovery from an attack accompanied by paralysis does not always lead to immunity. In one instance, he observed that a monkey

died of a severe poliomyelitis following the third re-inoculation, which took place  $4\frac{1}{2}$  months after the first, although typical paralysis had developed during the original illness. That this must be an unusual occurrence, however, is indicated by the fact that out of more than 1800 monkeys used at the Rockefeller Institute, in only 2 was an extension of paralysis observed as a result of the injection of a large dose of virus several months after recovery from one attack of the experimental disease (Amoss, A 18).

As monkeys do not survive long in captivity, the duration of immunity in these animals is difficult to determine (Levaditi, L 34), but it has been shown that it may persist for at least  $2\frac{1}{2}$  years (Jungeblut, personal communication).

In human poliomyelitis, it would seem that in the great majority of cases one attack confers a lasting immunity. Well authenticated instances of second attacks, however, have been reported (see *Chapter on Symptomatology*). This fact is by no means contradictory of the general principle, as in other such highly protective virus diseases as variola and varicella, second attacks have been known to occur. "Indeed it may be doubted whether any form of infection necessarily establishes permanent immunity" (Still, 1930, S 59).

**Neutralization in Vitro.** Levaditi and Landsteiner (February 19, 1910, L 46) were the first to show that the serum of monkeys that had recovered from the experimental disease neutralized the virus of poliomyelitis *in vitro*. Equal parts of a paper filtrate of virus emulsion and serum were used for injection after standing 4 hours at room temperature and over night in the ice-box. Similar results with convalescent monkey serum were reported by Leiner and von Wiesner (March 3, 1910, L 28, III), Römer and Joseph (March 15, 1910, R 28) and by Flexner and Lewis (seventh note, May 28, 1910, F 45); while Netter and Levaditi (April 9, 1910, N 8) and Flexner and Lewis (F 45) demonstrated the same property in the serum of human beings recovered from acute poliomyelitis.

### Distribution of Neutralizing Substances in the Body

**Blood.** By neutralization tests, antibodies have been detected in the blood of monkeys 36 hours after the onset of paralysis (Brodie, personal communication); in human blood as early as the third day (Kling and Levaditi, 1913, K 12); and by the sixth day or during the first week of illness (Clark, Fraser and Amoss, 1914, C 14; Flexner and Amoss, 1917, F 23); judging from the blood of those who have recovered from the disease they persist through life.



**Spinal Fluid.** In human spinal fluid immunity principles have been demonstrated, though infrequently, during the first 1 or 2 months of convalescence from poliomyelitis; after 1 or 2 years, neutralization with spinal fluid may take place, but is exceptional (Flexner and Clark, 1911, F 31; Flexner, Clark and Amoss, 1914, F 36). Spinal fluid from monkeys has never been reported positive except under the experimental conditions described below.

An aseptic inflammation of the meninges, induced by the intraspinal injection of sterile horse serum, has been shown to increase their permeability to immune bodies in the blood (Flexner and Amoss, 1917, 1918, F 23, F 26). In passively immunized monkeys, this passage took place in a short space of time, during the period, apparently, that the inflammation was at its height. Monkeys were given an intraspinal injection of normal horse serum, and 16 hours later, an intravenous injection of immune monkey serum. Fluid withdrawn at 6 and 9 hours (combined) had neutralizing power; the 24 hour specimen did not; neither did the fluid from the control that had received only the intraspinal injection of horse serum.

In actively immune animals, neutralizing substances were detected in the spinal fluid as early as 12 hours and as late as 48 hours after the intraspinal injection of horse serum. It was thought that this passage probably continued as long as the inflammation lasted.

**Nasal Secretions or Washings.** Fifty-six experiments on the neutralization of the virus of poliomyelitis by nasal washings were described by Amoss and Taylor (1917, A 24). The results indicated that such washings did neutralize active virus but that this power fluctuated, even in the same person. Inflammation of the upper respiratory tract removed or diminished the neutralizing power, though other irregularities occurred. The authors suggested that the presence or absence of this neutralizing property in the secretions might determine the development of healthy carriers. This property might also be an accessory element of defense against invasion by the virus.

**Brain.** The fate of the poliomyelitis virus in the brain of monkeys following intracerebral inoculation has already been considered (*Distribution of the Virus in the Body*; see also *Chapter on Pathology*). Brief reference may be made again to the fact that Jungeblut (1931, J 19) was unable to recover virus, injected into the brain of convalescent monkeys, from the site of inoculation at 12, 24, 72, or 96 hour intervals, although it was found in 2 instances at the 48 hour interval. The possibility of an inhibitory factor, which sterilized the site of inoculation in the immune animal, was considered.

**Bile.** Reference has already been made (under *Properties of the Virus*) to the fact that Leiner and von Wiesner (1911, Z 3) were able, in 2 instances, to neutralize virus with bile obtained from monkeys paralyzed as a result of the experimental disease. They suggested that immune bodies might enter the bile from the blood, although the number of tests was too small to justify a definite conclusion.

**Stools.** Levaditi, Kling, and Lépine (1931, L 43) found that they were unable to infect monkeys by the gastro-intestinal route with fecal matter rendered definitely virulent. They raised the question of absorption of the virus or of neutralization by virucidal principles in the excreta and proposed a study of these possibilities. As the possibility of producing infection by the gastro-intestinal route is still in doubt, the significance of the failure noted may be questioned.

### Distribution of Neutralizing Substances in the Animal Kingdom

Having determined that the blood serum of human beings and of monkeys that have recovered from poliomyelitis possessed the property of neutralizing the virus *in vitro*, it became of interest to learn whether other human or animal sera might also have this power. It has been shown that neutralizing or inhibiting substances are more widely distributed than was at first suspected.

#### Animals

**Monkeys: Normal.** It has generally been accepted that normal monkey serum does not neutralize the virus *in vitro* (Pettit, 1929, P 16; Aycock and Kramer, 1930, A 46; Shaughnessy, Harmon and Gordon, 1930, S 33). Recent work by Jungeblut and Engle (1932, J 21) would indicate that this statement must be modified; although serum from immature animals had no neutralizing power, sera from adult monkeys effected neutralization in some instances. Individual samples of serum from 16 normal rhesus monkeys of probable age between  $1\frac{1}{2}$  and 3 years all failed to neutralize.

“Quite different results, however, were obtained when normal sera of *adult* rhesus monkeys were studied. These animals were mature when received, judging not only from size but from development of the teeth and sexual organs. The males carried the testicles in the scrotum and the females were passing, more or less regularly, through definite cycles of menstruation. They were kept in separate quarters belonging to the Department of Anatomy and were never in contact with the infected animals nor the attendants handling them. We had an opportunity to test the serum of seven of such animals, one male and six



females, for neutralizing power against poliomyelitis virus. Two of these animals were bled twice so that the samples under investigation numbered nine in all. Four of these nine samples were found to neutralize the virus *in vitro* perfectly, the remaining five exerted no demonstrable virucidal action in the quantities tested. The four neutralizing sera came from four different female animals and were all obtained within ten days *after* onset of menstrual bleeding. Two of these animals when bled again a few days *before* onset of the next menstrual cycle gave sera which failed to neutralize. We do not know whether this fluctuation in virucidal power of the serum in the same animal is causally related to the various phases of menstruation or has been due to other factors. Work is under way to investigate more precisely the above mentioned possibility in the human."

Although transmission of the experimental disease to a *Cebus* monkey has been reported in one instance (Flexner and Lewis, 1910, F 47), the South American species have usually proved less susceptible than the monkeys from the Old World (Flexner and Lewis, F 47; Kraus and Kantor, 1917, K 31) (see also *Susceptibility of Monkeys* in the *Chapter on Etiology*). To quote again from Jungeblut and Engle:

"The mechanism of this natural resistance, however, has remained obscure. In this connection it is interesting to point out that the *Cebus* monkey does not show evidence of a menstrual cycle or periodic bleeding similar to the macaque or human beings. We have attempted to infect four *Cebus* monkeys by intracerebral inoculation with poliomyelitis virus without producing any symptoms of the disease. Moreover, the animals remained refractory to repeated inoculation after they had been subjected to splenectomy and bilateral castration. Normal sera obtained from these monkeys before inoculation were tested for neutralizing power in the usual manner. Of the four sera, three neutralized the poliomyelitis virus. The one serum which failed to neutralize was not retested; however the animal proved equally insusceptible to intracerebral inoculation."

Moreover, even immature rhesus monkeys proved resistant to intracerebral inoculation after treatment with anterior pituitary extract and the resultant acceleration of maturity; in a few cases the serum showed slight neutralizing power (Jungeblut, 1932, J 22).

**Convalescent.** Although convalescent monkey serum usually effects neutralization, occasional irregularities have been reported. Leake (1918, L 18) reported 1 failure to neutralize virus with serum withdrawn from a monkey 1 month after a typical attack of the experi-

mental disease. Nine failures were described by Aycock and Kramer (1930, A 46); 2 sera were not retested; the other 7 failures were with samples obtained from 4 monkeys but, in each instance, in a subsequent test either with the same sample or with that from a different bleeding, neutralization was effected.

**Actively Immunized.** The results of neutralization tests with sera of monkeys that have been actively immunized are given in the *Section on Active Immunization*. In this group, the neutralization test has been found to be a more delicate test of immunity than re-inoculation; monkey serum may neutralize virus *in vitro* although the actively immunized animals from which it is obtained are not able to resist an intracerebral injection of potent virus.

### Refractory Animals

**Normal.** In some instances, normal sera from insusceptible animals have been shown to have an inhibitory effect on the poliomyelitis virus in neutralization tests. The results, however, are not constant even for the same species. The natural inhibiting effect of sheep serum has been demonstrated by a few workers (Flexner and Lewis, 1910, F 46; Stewart and Haselbauer, 1928, S 56), though others have obtained only negative results (Kraus, 1911, K 27; Howitt, 1932, H 35; Jungeblut and Engle, 1932, J 21).

In one instance reported by Schultz and Gebhardt (1931, S 15) normal horse serum neutralized equivalent amounts of the virus in a final serum dilution of 1:2 but not in a dilution of 1:4. The possibility of obtaining neutralization with normal goat serum has been mentioned by Howitt (1932, H 35).

**Actively Immunized.** The results obtained with sera of refractory animals that have been immunized for the purpose of preparing a therapeutic serum are described later in the *Section on Immune Sera*.

### Human Beings

**Normal.** The results of neutralization tests with sera from normal persons are discussed at length under *Latent Immunization*, *Chapter on Epidemiology* and the titer of normal human sera as compared with that of convalescent sera is taken up later in this chapter under *Immune Sera*. It is only necessary here, therefore, to state that neutralizing substances have been found to be widely distributed among normal individuals both of northern and southern communities; they



do not appear with much greater frequency in the sera of persons that have been in direct contact with the disease than in sera from individuals that have had no direct exposure as far as known. Neutralizing substances are, however, found more frequently in the sera of the individuals of urban than of rural communities, and in increasing frequency with age in both groups. Passive transfer of immunity from mother to infant has also been suggested by neutralization tests.

Such a widespread distribution of virucidal properties in the sera of healthy persons led Kling and Levaditi (1913, K 12; see also Levaditi, L 36) to express the "opinion that immunity was due to latent infections, the organism reacting to the virus only by the production of antibodies." This theory has been supported by Müller (1922, M 54) and, in particular, by Aycock and Kramer (1930, A 46).

However, even in communities where poliomyelitis is seldom observed clinically and where the possibility of exposure to the virus might thus seem to be comparatively slight, as in the Virgin Islands and in Porto Rico, neutralizing sera have been obtained (Shaughnessy, Harmon and Gordon, 1930, S 33; Soule and McKinley, 1931, S 50). Even more noteworthy is the fact that in 3 instances, blood sera from 3 normal adult Eskimos have been found to effect complete neutralization (Jungeblut, 1932, J 20b). These sera were obtained by Dr. Heinbecker from Eskimos in Robertson Bay in 1928. All belonged to blood group O. Two of the sera also contained diphtheria antitoxin. Six of the 10 Chinese sera which failed to neutralize the virus of yellow fever (Sawyer and Hughes, S 6), have also been tested against the poliomyelitis virus (Jungeblut, J 20b) and, in each case, complete neutralization was obtained.

In the course of an investigation into the specificity of the "neutralization test," N. Paul Hudson and Edwin H. Lennette (personal communication; paper to be presented before the Epidemiological Section of the American Public Health Association in Washington, D. C., on October 24, 1932) "examined the serum of 20 Liberian negro natives working inland on the Firestone rubber plantations. Eighteen neutralized the virus, 1 did not, and 1 test animal died early of an intercurrent infection, using the serum undiluted. An inquiry into the occurrence of the disease led to no very satisfactory results so far as Liberia is concerned. Cases in natives are reported from neighboring West African colonies and it is possible that the same may be true of Liberia."

Other facts with regard to the inhibiting power of certain normal sera have recently been emphasized and present interesting features; the

greater degree of protection afforded by sera (both normal and convalescent) from blood group B than by those from other blood groups; variations in protective power with relation to the menstrual cycle and also the possibility of a relation to the hormone production associated with pregnancy. These subjects are all discussed at length under *The Host* in the *Chapter on Epidemiology*.

### Convalescent

**Abortive Cases.** The occurrence of abortive cases was apparently demonstrated experimentally by Netter and Levaditi (1910, N 9). The sister (age not given) of a patient with typical poliomyelitis showed lassitude and general symptoms but not paralysis. The serum was found to possess neutralizing power 6 weeks after the attack. This evidence is, to be sure, inadequate as there is no way of proving that neutralizing substances were absent before the illness.

The sera of cases thought to be of the abortive type have since been studied for the presence of antibodies by a number of workers but thus far the results have been inconclusive. It must be remembered that in much of the earlier work nonparalytic cases were often called abortive. Present usage, however, limits the term abortive to those cases that show no evidence of involvement of the central nervous system. Anderson and Frost (1911, A 26) obtained serum from 9 cases of suspected poliomyelitis without paralysis (so-called abortive cases) during an epidemic of the disease. In 6 instances active virus was neutralized *in vitro*. It may be noted, however, that these patients were all adults and that the 3 sera that failed to neutralize were obtained from young persons (16 years or younger). It has been pointed out by Shaughnessy, Harmon, and Gordon (1930, S 33) that the results may have been "nullified . . . by the addition of 'normal' human serum to activate the serum-virus mixtures" and that Netter and Levaditi had likewise "added an unknown variable by using 'normal' human serum."

Peabody, Draper, and Dochez (1912, P 7) were able to effect neutralization with only 1 of 3 sera from suspected abortive cases. Müller (1911, M 53), working with Römer, and Fairbrother and Brown (F 5) each found definite evidence in single instances of neutralizing properties in the sera of such cases.

A larger series has recently been reported by Kramer and Aycock (1931, K 24). Immunity tests were performed on 20 children that showed symptoms of mild illness (unexplained headache, fever, vomiting, for 24 to 48 hours) during the period that 5 cases of frank poliomyelitis



developed in the same school. The children were selected to include blood samples from each school age group. Two groups of controls were also tested. One consisted of 28 children of corresponding ages that attended this school but that had shown no recognizable illness at the time. The other group was selected from school children in an adjacent town where no cases of poliomyelitis had been observed. The blood was collected about 5 months after the outbreak in order to allow time for the development of immunity. The results of the neutralization tests in these three groups were identical; those that had passed through the mild illness showed no higher rate of immunity than did the controls.

The most convincing evidence of the existence of abortive cases has been furnished, however, not by immunity tests but by the recovery of the virus from oral washings made in the early stage (Paul and Trask, 1931, P 5). This work is discussed under *Symptomatology*, and also under *Distribution of the Virus*, in the *Chapter on Etiology*.

**Frank Cases.** Although human serum, obtained after an attack of poliomyelitis is usually effective in neutralizing the virus, there may be wide variations in potency and, in certain instances, inhibitory power may be completely lacking. The factors influencing potency are taken up later under *Immune Sera*. Mention may be made here, however, of certain failures that have been observed. For example, Netter and Levaditi (1910, N 9) did not succeed in completely neutralizing virus with convalescent serum obtained from a patient 11 years after the acute attack, and 1 monkey in a series studied by Taylor (1919, T 4) for differential blood counts had developed the disease after an incubation period of 30 days, although inoculated with a mixture of virus and "human immune serum." Certain failures with human convalescent serum were noted by Ayccock and Kramer (1930, A 46). Two specimens that failed to neutralize were obtained 30 years and 6 months after the acute illness; others were samples of pooled serum. Three of the 14 specimens of convalescent sera tested by Shaughnessy, Harmon, and Gordon (1930, S 33) failed to neutralize in any dilution. Schultz and Gebhardt (1931, S 14) and Jungeblut and Smith (1932, J 27) have also obtained negative results in some instances.

Whether these results indicate that such individuals might be susceptible to re-infection with a virulent strain cannot be determined. The infrequency of second attacks would argue against such a supposition. In the case of other viruses, it has been observed (Rivers, 1927, R 18a) that "the degree of active immunity usually exhibited by individ-

uals recovered from virus diseases, seems disproportionate to the amount of passive protection afforded by their sera."

**The Neutralizing Substances: Their Properties and Nature.** In their ninth note (1911), Flexner and Clark (F 21) referred to the immunity principles as "probably of the nature of antibodies" but until recently, relatively little effort was made to determine their properties more exactly.

In studies on the neutralization of the poliomyelitis virus by nasal washings, Amoss and Taylor (1917, A 24; Vermont Report, 1924), determined certain facts concerning the neutralizing substances. Fractional sterilization and filtration of the washings through Berkefeld filters did not remove these substances. They were, however, rendered inactive by heating to 70°C.; they were evidently not volatile as neutralization was obtained after concentration *in vacuo* at 60°C.; they were also found to be water-soluble and were, apparently, not inorganic; their action did not depend upon the action of mucin as such (see *Immune Horse Serum*).

Although some of the earlier investigators had believed that fresh complement was necessary for neutralization (Landsteiner, 1913, L 4), Flexner and Amoss (1918, F 26) determined that the neutralizing substance acted directly upon the virus without reactivation. This fact has been reaffirmed recently by Fairbrother (1930, F 4).

It has been shown that neutralization of vaccine virus with immune serum does not destroy the virus (Todd, T 14; Andrewes, A 29; Long and Olitsky, L 65). Active poliomyelitis virus, too, has been recovered by cataphoresis, from a neutral serum-virus mixture (Olitsky, Rhoads, and Long, 1929, O 2). These authors "conclude that the virus is not killed by the anti-serum, but only held in some sort of an ineffective combination."

Schultz, Gebhardt, and Bullock (1930, 1931, S 16, S 17) too, found that neutral serum-virus mixtures were dissociable. Such a mixture was rendered infective by the addition of a suitable quantity of physiological saline immediately before injection. "These observations," they conclude, "indicate clearly that the inactivation of poliomyelitis virus by immune serum resembles more closely a toxin-antitoxin reaction than a bactericidal type of reaction."

The effect of *time* on the inactivation of virus by immune serum was studied by the same authors. They had found, as had other observers, that if undiluted immune serum was used, it was not necessary to incubate the serum-virus mixture before injection. But if the immune



serum was diluted, longer contact between the two reagents was required. Schultz and his associates refer to the opinion held by other workers with the ultramicroscopic viruses that immune sera do not act directly on the infectious agents but in some way alter the susceptibility of the tissues. They conclude, however, that "the fact that with dilution of immune serum it becomes necessary to prolong its contact with the virus *in vitro* argues distinctly in favor of the opinion that the immune serum *does not act directly on the virus.*"

It has been observed, moreover, that the quantity of the inoculum rather than the potency of the virus determines the amount of a specified serum needed to neutralize it (Weyer, Park, and Banzhaf, 1931, W 17). With particularly potent strains, the virus preparation may contain several hundred killing doses.

The specific nature of the neutralizing antibodies has recently been questioned by Soule and McKinley (1931, S 50) and by Jungeblut (J22, J27, J20a). It was found by the former that the sera of 8 normal Porto Rican adults proved effective in neutralizing a potent virus although, according to the authors, no cases of poliomyelitis, originating on the Island, had been proved by autopsy (see, however, Morales, M 44; and Chapter on *Epidemiology*). These workers question whether the neutralizing substances are true antibodies or whether such phenomena should "be classed under the head of 'physiological immunity.'" They refer in this connection to the work of Friedberger, Bock, and Fürstenheim (1929, F 66) who concluded that "'antibodies' against all possible noninfectious antigens which do not penetrate the body are formed exactly as those against diphtheria toxin and in exactly the same relationship to age" and thus who supported the view of Friedberger and Heim (1929, F 67) that "in the development of the diphtheria curve in various age groups, we are dealing not with the consequence of a latent or manifest infection but with a phenomenon that is part of a universal biological occurrence." As shown by tests on Eskimos (Bay-Smith, B 9) diphtheria "antibodies" may develop in man even when previous contact with the diphtheria bacillus has been ruled out. Whether this may be true of poliomyelitis protective substances has not been definitely determined; mention has been made of positive neutralization tests with Eskimo sera and Liberian sera. Direct experimental evidence has been afforded by studies recently described by Jungeblut and Engle (1932, J 22). In a number of experiments a percentage of immature monkeys was protected partially or completely against intracerebral inoculation by a series of preliminary injections of anterior

pituitary extracts or implants. After hormone treatment maturity was accelerated and the serum of these monkeys occasionally acquired definite though slight neutralizing power. Complete neutralization was also obtained occasionally with the serum of adult monkeys, as previously described. The above authors suggest that the protection against poliomyelitis exhibited in adult life is due not so much to latent immunization as to the normal endocrine balance characteristic of physiological maturity.

Other possible constitutional factors in the resistance to poliomyelitis have been emphasized by recent experiments. Hirzfeld, Hirzfeld and Brokman (1924, 1927, H 26, H 25) had shown that response to the Schick and to the Dick reactions is, to some extent, inherited in correlation with the blood group. Evidence has recently been brought forward to show that persons belonging to one particular blood group (Group B) are apparently more resistant to poliomyelitis than members of the other groups (Jungeblut and Smith, 1932, J 27).

The results above mentioned and especially the fact that the protective power of the serum from a given individual may vary with the physiological function of menstruation (Jungeblut, 1932, J 20a) suggest that the inhibiting substances may, in some instances, at least, be non-specific in character. The relation of such possible nonspecific inhibiting substances to specific immune bodies can, at the present stage of our knowledge, be only a matter for conjecture.

Zinsser (1931, Z 7a) has referred to the nature of the "protective bodies" in ultramicroscopic virus diseases as "quite uncertain." Although spoken of as antibodies, "it is clear . . . that there are certain important differences between the classical bacterial antibodies and these protective reaction products to virus infection." In virus diseases, other than poliomyelitis (and in poliomyelitis as well), virus and protective bodies have been recovered separately from neutral mixtures, thus showing that the protective substance is not virucidal. "There is no antigen-antibody union, therefore, comparable to that observed with bacterial antibodies." In the case of virus III and vaccine virus, Andrewes (1929, A 30) has concluded that "it seems possible that the immune serum acts by preventing the virus from entering the cell, and that if it has failed to achieve this purpose, it is powerless to do anything else."

In poliomyelitis, as in other virus diseases, immunity, once acquired, is apparently permanent. In a discussion on vaccine virus, Winkler (1925, W 26) suggested, and his hypothesis has been accepted by some,



that the lasting immunity may be due to the persistence of the living agent in the body. No experimental proof of such a persistence of the poliomyelitis virus has as yet been provided (see *Persistence of the Virus, Chapter on Etiology*).

**Specificity of the Reaction of Neutralization.** By neutralization tests, Landsteiner, Levaditi and Pastia (L 8, L 34) proved that there was no biological connection between rabies and poliomyelitis. Inoculation tests have been used to show that experimental enzoötic encephalomyelitis (Borna's disease) is also distinct immunologically from poliomyelitis (Nicolau, Galloway, and Stroian, 1929, N 27). Because an outbreak of acute encephalomyelitis occurred among the horses and mules in California in 1931 simultaneously with an epidemic of poliomyelitis, cross-immunization experiments with both viruses were undertaken by Howitt (1931, H 34). The results of *in vitro* neutralization tests and of direct inoculation tests showed that no cross immunity occurs between the two viruses.

The specificity of the reaction has also been shown for the human disease by comparison with epidemic encephalitis (Amoss, 1921, A 15; Levaditi, 1929, L 35). Amoss showed experimentally that sera of patients convalescing from epidemic encephalitis, when given intraspinally, did not protect against poliomyelitis virus given intravenously, while convalescent monkey serum did so protect. Levaditi was unable either to vaccinate a monkey with herpetico-encephalitic virus against the virus of poliomyelitis or to vaccinate a rabbit with the virus of infantile paralysis against that of encephalitis. Both of these authors concluded that these two diseases were immunologically distinct. According to Jungeblut (personal communication) herpes virus was not inactivated by poliomyelitis neutralizing sera and vice versa.

The biologic identity of the disease as it occurs in different epidemics and in various parts of the world (Vienna, Paris, Germany, England, and several sections of the United States) has been suggested by the results of immunity tests (Netter and Levaditi, N 8; Leake, L 18; Levaditi, L 34; Fairbrother, personal communication). Burnet and Macnamara (1931, B 42), however, found distinct immunological differences between a local (Victoria, Australia) virus and the Rockefeller Institute "mixed virus." These differences were demonstrated by cross-immunity experiments and by neutralization tests *in vitro*. In 3 instances, monkeys developed the typical, fatal disease after injection of the M.V. virus although they had recently recovered from a typical attack induced by the Victoria virus. The question arises here whether the M.V. virus

may not have been altered by long passage as observed recently by Weyer (1931, W 16) for other strains adapted to monkeys (see *Strains, Chapter on Etiology*).

Thus the immunological difference observed may be one between a human virus and a virus altered by animal passage and not a difference between two human strains. Comparison of the Victoria virus with recently isolated New York strains will be interesting and is now possible as Dr. Macnamara has been able to send a specimen of the Australian virus to the Rockefeller Institute (personal communication).

**Allergic Reactions.** Römer and Joseph (1910, R 29) suggested that a period of hypersensitivity might precede immunity. In one instance a monkey, re-inoculated 17 days after the first injection, proved more susceptible than the control. A similar phenomenon has since been observed to be of frequent occurrence in experimental work (Flexner, 1910, F 11; Flexner and Amoss, 1917, F 25; Pettit, 1929, P 16; Shaughnessy, Harmon and Gordon, 1930, S 32; Rhoads, 1930, R 9; Flexner, 1931, F 20). It would seem, as Amoss has stated (A 18) that "the injection of subinfective doses does not confer a refractory period but apparently renders the monkeys more susceptible." Such a reaction has been noted in the course of experimental immunization, both when repeated small doses of virus have been injected intradermally or subcutaneously (Rhoads, 1930, R 9) and when heated virus has been injected intracerebrally (Shaughnessy, Harmon and Gordon, 1930, S 32). It has been suggested that repeated injections (intracerebral and intraperitoneal) may afford a method of adapting to monkeys certain human strains that otherwise are not readily implanted (Flexner, 1931, F 20).

Evidence of a possible anaphylactic reaction has been furnished by the experiments recently reported by Brebner (1932, B 28). In 3 groups of monkeys, one consisting of immune convalescent monkeys, one of animals experimentally immunized, and the third of monkeys that had shown a natural immunity, intrasplenic or intraperitoneal injection of virus invariably produced death. Death was either sudden, usually while an intrasplenic injection was in progress, or, if lingering, it occurred some days after an intraperitoneal inoculation. The reaction took place only when 47 days or more had elapsed since the immunization had been started or the abortive infection had developed. Intrasplenic injection of normal nerve tissue had no effect on the 2 animals tested; one of these was reinjected with virus 5 days later and died immediately. Brebner is inclined to attribute the reaction described to an interaction



of the virus antigen and antibody although the possibility of sensitization to some protein degeneration produced in the nerve tissue as a result of virus action, is considered.

As a result of a study of the febrile reaction observed in monkeys reinoculated with the virus, Jungeblut (1931, J 18, J 19) has suggested that "sensitization in poliomyelitis may be of frequent occurrence." Convalescent monkeys, reinoculated intracerebrally, responded with an almost immediate and marked febrile reaction. Subcutaneous or intracerebral injection of killed virus produced a similar accelerated reaction. No reactions were obtained after injection of normal brain or cord. Temperature curves of monkeys that had received a course of injections of live virus by different routes for the purpose of artificial immunization, showed upon intracerebral inoculation with virus, an unusually early and prolonged elevation. Jungeblut has called attention to the close analogy between these accelerated febrile reactions and those observed in human allergic phenomena, such as anaphylaxis, serum sickness, and the tuberculin reaction. This sensitization may be due to the pathologically changed brain substance rather than to the virus itself.

Neither Römer (R 25) nor Leiner and von Wiesner (L 28, IV; Z 3) were able to find evidence of hypersensitiveness as shown by a cutaneous reaction analogous to the Von Pirquet tuberculin test. Jungeblut was also unable to produce local reactions in convalescent monkeys but has recently (1931, J 18a) reported the results of intracutaneous injection of killed virus in 27 human convalescents (3 to 22 years old). In all, local redness and swelling developed which increased in intensity from the fifth to the twenty-fourth hour. The specific reaction was read during the 24 to 48 hour interval and consisted of an erythema, usually 3 to 4 cm. in diameter, with a lighter area surrounding a darker center in about half of the cases. Subcutaneous injection of killed virus also produced a marked local reaction, but no general reaction in the 2 convalescent children tested. No reactions comparable to the virus reactions were obtained with control material (normal cord) in this series, although urticarial reactions which lasted for 2 hours occurred in some children. These reactions were felt to indicate the same state of allergy against the virus in the human convalescent as was shown by the accelerated febrile reaction in monkeys.

Recent work by Sabin (personal communication to Dr. Park) indicates that this is not a sensitization to the virus but to other substances accidentally accompanying it. No evidence of an allergic skin reaction was obtained in normal adults or in convalescents, either recent

or of long standing, when tested with fresh heat-inactivated preparations of monkey virus, human virus (1931), and normal monkey cord. In some instances, with older preparations, either of virus or normal material, a slight skin reaction was obtained; in these preparations histamine-like products were demonstrated by the guinea-pig uterus strip method. Such a reaction, observed in normal adults with control material may, in Jungeblut's opinion, be comparable to a pseudo-Schick reaction. Further study as to the significance and specificity of these tests is in progress.

Sabin also found that virus preparations, concentrated after purification by adsorption and elution, gave marked delayed skin reactions. Normal cord, prepared in the same way, gave similar results. These reactions, however, may possibly have been due to irritation by the chemicals used in the process of purification.

### Complement Fixation Tests

**Spinal Fluid.** While Wollstein (1908, W 28), Gay and Lucas (1910, G 5), and Römer and Joseph (1910, R 28, R 25) early reported negative results with complement fixation tests on spinal fluid, Kolmer and Freese (1916, K 20) and Neustaedter and Banzhaf (1917, N 15) obtained a certain proportion of positive tests.

With aqueous extracts of poliomyelitic central nervous system tissues as antigens, Kolmer and Freese observed 6 to 16 per cent weakly positive reactions with the spinal fluids from 130 patients, and 15 to 17 per cent positive reactions with extracts of poliomyelitic liver and spleen. With large doses of bacterial antigens, a small percentage (6 to 9) of weakly positive reactions was observed with the spinal fluids of 35 persons. The results were considered too irregular to be of value in diagnosis.

**Blood Serum.** Although neutralizing substances are found only exceptionally in the spinal fluid but regularly in the blood serum (of immune persons and animals), the reverse would seem to be true of complement fixing bodies, at least, in so far as they are found at all.

Lebrede and Recio (1910, L 22) reported 1 positive reaction with 3 human sera tested. Although Kolmer and Freese (K 20) obtained 2 to 4 per cent of positive reactions with antigens from poliomyelitic tissues, the results with all bacterial antigens were entirely negative. Thus their observations indicated "that the antibody or reactionary substance concerned is more easily detected in spinal fluid than in serum."

Aside from these isolated positive results and the fact that Eckert



(1911, E 5) and Schottmüller (1912, S 10) obtained positive Wassermann reactions in a few cases of poliomyelitis (4 each), all other reported results of complement fixation tests with poliomyelitic blood serum have been negative (Wollstein, W 28; Gay and Lucas, G 5; Römer and Joseph, R 28; Schultz, Gebhardt, and Bullock, S 16, S 17).

Römer and Joseph noted that, in addition to other negative tests, serum from monkeys immunized with large doses of virus failed to fix complement, although this serum was used successfully in neutralization tests. They did, however, obtain fixation with serum of a sheep that had received many injections of virus. But this serum also gave a positive result with antigen from a normal monkey cord. The reaction was thought therefore to be merely one between the albumin of the sheep serum and that of the monkey cord.

The fact that the reported positive results of complement fixation tests on spinal fluid and the negative results on blood serum did not correspond with the recognized distribution of the virucidal substances, suggested to Schultz, Gebhardt, and Bullock that this was a nonspecific reaction and not an interaction between the specific antibody and the virus. They made, therefore, a more extensive study of the complement-fixing properties of sera of known neutralizing power. The antigens were prepared from a virulent poliomyelitic monkey cord and medulla; a 5 per cent suspension in physiological saline; the ether-soluble and the ether-insoluble fractions of ground poliomyelitic cords; and a trypsinized suspension of virus material.

None of the 21 sera from convalescent and hyperimmunized monkeys gave fixation with any of the antigens. Nine of these sera had been previously tested for virucidal antibodies. As the presence of these substances was easily demonstrated in that number, it was felt that all undoubtedly possessed neutralizing properties.

Identical negative results were obtained with 4 specimens of human convalescent serum and 10 specimens from normal adults. All had been proved to be virucidal in *in vitro* tests; some of the normal sera neutralized in a dilution of 1:30.

Tests were carried out also with poliomyelitis refractory animals (guinea pig, rabbit, dog, sheep, and goat), which had received injections of virus (monkey cord and medulla) over long periods of time for the purpose of immunization. Sera from these animals had been examined for virucidal action (Schultz and Gebhardt, 1930, S 13). In some instances, neutralization had been obtained with undiluted serum but not in a final dilution of 1:4, although monkey convalescent serum was effective

under the same conditions in a dilution of 1:64. Observations on this group, therefore, were considered less significant than those on the two preceding groups. No important differences were noted in the degree of fixation with virus or virus-free antigens. In the case of rabbits, a reaction did occur in several instances. This was thought, however, to be nonspecific, for the serum of rabbits immunized against poliomyelitic monkey cord was shown to react not only with monkey antigens but with antigens from other animals.

**Precipitin Tests.** Precipitin tests with sera were reported by Schultz, Gebhardt, and Bullock (1930, S 16, S 17). Three antigens were used and tests were made on immune sera from the groups described above. No evidence of precipitins specific for the virus could be obtained.

The results of complement-fixation and precipitin tests indicated to these investigators "that the antibodies responsible for this inactivation of poliomyelitis virus resemble antitoxins more closely than they do bactericidal antibodies."

It may be mentioned here that most of the antitoxin in horse serum is contained in the pseudoglobulin concentrate. Weyer, Park and Banzhaf (1931, W 17) found that about 50 per cent of the poliomyelitis antibody in antipoliomyelitic horse serum was associated with this protein fraction. Morgan and Fairbrother (1930, 1931, M 46, F 8) concluded, on the other hand, that the antiviral substances were present in greatest concentration in the euglobulin portion (see *Serum of Refractory Animals*).

**Stabilization Test with Gold Chlorid.** Jungeblut (1930, J 17) observed that poliomyelitis monkey serum prevented the precipitation of tissue emulsions by a gold chlorid solution while normal monkey serum did not. Of 66 poliomyelitic sera, 81.8 per cent afforded complete stabilization, while none of 23 normal sera stabilized completely. In 10 instances, a characteristic change in the serum reaction was noted before and after the infection. Only 4 per cent of the human sera examined lacked stabilizing properties completely; no fundamental difference between the sera of adults and of children was observed. In one experiment, the results of neutralization tests appeared to support the hypothesis that the stabilizing property of the serum may be an index for susceptibility in the human being. No conclusion was reached with regard to the phenomenon described, whether it was an antigen-antibody reaction or a nonspecific increase in the protective colloidal properties of the serum.



**Colloidal Gold Test.** Although Eberson (1931, E 3) stated that the results obtained with the above method were neither specific nor consistent, no figures were given. A test was then described (Eberson, E 3; Eberson and Mossman, E 4) for the "detection and titration of immune bodies in poliomyelitis," using colloidal gold, sodium chlorid, and serum. Although based on the same principle, the results were felt in this case to be decisive. Immune human and monkey serum gave a rose-colored or violet precipitate with gradations of color in the supernatant fluid (for example, 1111224477). Tubes with the lower dilutions of serum showed the most marked precipitation.

The above authors examined a total of 363 sera; 100 from normal adults, 100 from normal children (6 weeks to 19 years), 58 convalescent sera (human and monkey), 76 from normal animals (monkey, horse, goat, and sheep), and 29 from immunized animals (monkey, horse, goat, and sheep). The results corresponded with the expected distribution of neutralizing substances in such sera. Of the 100 normal adults, a positive test was obtained in 64 per cent; of the 100 children, a negative test was obtained in 77 per cent.

This test was thought to be of prognostic value. In cases that made a good recovery, there was a progressive development of the immune bodies as indicated by this method, but in cases with a poor outlook they could not be demonstrated.

The specificity of the test was demonstrated, according to Eberson and Mossman, by *in vitro* neutralization experiments: sera with a positive colloidal gold test were shown to neutralize virus but sera with a negative reaction did not. Moreover, immune serum-virus mixtures, in which the virus was present to excess, did not precipitate the colloidal gold preparation, but when the antibodies were in excess, the serum gave a positive precipitation test.

The authors believe the colloidal gold test to be of practical value in the selection of a potent human or animal serum, either for therapeutic or experimental purposes, in a study of susceptibility to the disease, and in giving a prognosis. (For colloidal gold test on spinal fluid see *Section on The Experimental Disease.*)

### ACTIVE IMMUNIZATION

In view of the low morbidity rate of poliomyelitis, widespread active immunization of human beings would probably never be attempted, even if a method of proved success were available. During epidemic periods, however, any means that offered a possibility of controlling

the spread, would be eagerly sought. A great variety of experiments has been carried out in the attempt to produce immunity in monkeys, but thus far no method has been found that could be tried with safety for the prevention of the human disease.

**Killed Virus.** It has been found true of most filterable viruses that "active immunity can be attained only when some degree of reaction to the living virus has occurred" (Zinsser and Tang, 1926, Z 8). Virus heated to 55°C. or over for varying periods—30 minutes to 1 hour—has been found to be completely inactivated (see *Properties of Virus*). Subcutaneous injection of virus thus treated has proved harmless but ineffective in the production of immunity (Flexner and Lewis, fourth note, 1910, F 42; Landsteiner and Levaditi, 1910, L 45, L 6; Römer and Joseph, 1910, R 27, R 25; Levaditi and Danulesco, 1912, L 40; Abramson, 1917, A 3; Abramson and Gerber, 1918, A 6). The last mentioned workers, it is true, obtained partial success with 10 injections of virus heated at 55°C. for one-half hour. Whether each sample injected was completely inactivated by this treatment cannot be definitely determined.

**Attenuated Virus.** In certain instances, immunity has been induced by the administration of virus modified under conditions which do not completely destroy the virulence.

*Attenuation by Heat.* Some degree of success with this method has been reported by a few authors. Römer and Joseph (1910, R 27, R 25) found that virus heated to 45°C. had definite immunizing power when given subcutaneously but that it did not have the necessary degree of safety; at 50°C., however, both requirements were apparently met. Levaditi and Landsteiner (L 34) confirmed Römer's results at 50°C. They felt that modification at this temperature was probably quantitative rather than qualitative (see Oluf Thomsen).

While Römer was able to test only a very small number of monkeys (5), Abramson and Gerber (1918, A 6) reported a somewhat larger series. On 5 successive days, 11 monkeys were injected subcutaneously with 5 cc. of a 10 per cent cord emulsion. On the first 2 days the emulsion was heated at 55°C. for 30 minutes; at 45° and 37°C. on the third and fourth days, and injected without preliminary heating on the fifth day. All of the animals remained well. Three weeks after the series of injections had been completed, 8 of the monkeys were given an intracerebral injection of from 3 to 6 fatal doses of virus; 5 resisted this test. Blood serum was obtained at the same time. Neutralizing substances were shown to be present in 7 of the 8 sera. In 3 instances



the serum completely neutralized the virus in the proportion of 1 part serum to 1 part 5 per cent virus. In 4 instances the incubation was prolonged, indicating partial neutralization.

By far the largest series of tests with heated virus has been reported by Shaughnessy, Harmon, and Gordon (1930, S 32). A total of 24 monkeys and 5 controls received a single preliminary inoculation and 2 were given multiple inoculations. In the first group, the inoculation was made intracerebrally with filtrates heated at temperatures varying from 42.5° to 55°C. for from 5 to 60 minutes.

Only 3 of the 24 showed an appreciable degree of immunity to a subsequent (31 to 40 days) intracerebral inoculation with active virus. The 3 relatively immune monkeys had received virus heated at 55°C. for 60 minutes, at 50°C. for 45 minutes and at 45°C. for 30 minutes, respectively. Of the 5 controls only 1 was definitely paralyzed, 2 had possible abortive cases, and 2 remained well.

In the second group of experiments, an attempt was made to immunize 8 monkeys by repeated inoculation of virus filtrate, heated to 50°C. for 30 minutes for the first 5, to 45°C. for 3, and to 42.5°C. for 3. In 6 instances, the injections were made subcutaneously and in 2, intracutaneously. Both of the monkeys that were inoculated intracutaneously recovered from the intracerebral test inoculation but only 1 of the 6 that received subcutaneous injections resisted the first immunity test. It was suggested that the intracutaneous method might be useful in the immunization of animals for convalescent serum (see later section).

Shaughnessy and his co-workers attributed their failure to induce an appreciable degree of immunity with heated virus to two factors. For the purpose of safety, they had used small amounts of a relatively weak virus preparation over a long period (2½ months) instead of large amounts or more active material. Then, too, a longer interval was allowed to elapse between the final immunizing injection and the test for immunity. Previous workers may have *happened* to make this test during the refractory period.

*Attenuation by Drying.* The first successful experimental vaccination against poliomyelitis was effected by means of the subcutaneous injection of dried cord by the Pasteur method for the prevention of rabies (Landsteiner and Levaditi, January 10, 1910, L 45, L 6, L 34). Two monkeys treated by this method developed immunity as shown by the resistance to a test injection (in 1 case combined intracerebral and intraperitoneal inoculation of virus; route not stated in the other

case), 10 days and 19 days after the final vaccination injection. Two other monkeys, however, contracted the disease during the course of treatment. Thus vaccination by this means, Levaditi concluded, though possible, was not practicable.

More recently, Aycock and Kagan (1927, A 44) attempted to vaccinate 7 monkeys by giving daily serial injections of active cord dried over caustic potash for periods varying from 26 days to 1 day. One monkey died of tuberculosis and 2 became paralyzed during the course of the immunizing injections. On subsequent (intervals 25 days to 4 months) intracerebral inoculation of active virus, 2 monkeys were found to be immune, and 2 proved to be susceptible.

#### *Attenuation by Chemicals*

*Phenol.* Kraus (1910, 1911, K 27) was the first to produce artificial immunity with chemically treated virus. In his first publication, he reported that, by means of 1 or 2 subcutaneous injections of virus treated with 0.5 per cent phenol, 2 monkeys were protected against a subdural injection of concentrated virus, given 10 days later. In the next paper, the author described further experiments to determine the optimum concentration of phenol and concluded that a single subcutaneous injection of 1 to 1.5 per cent carbolized virus was not only innocuous but afforded protection and that this method might be used for prophylactic vaccination in man.

Leiner and von Wiesner (L 29; Z 3) and Landsteiner and Levaditi (L 34) were unable to verify this work. Infection resulted either from the vaccination or from the test inoculation.

Later, however, Kraus (1930, K 29) confirmed his earlier work. Subcutaneous injection of 3 to 5 cc. of a 1 per cent phenolized virus produced no symptoms in 6 monkeys; 2 others developed a localized paralysis but survived. All were immune to a subsequent (1 to 2 months interval) intracerebral and intraperitoneal injection. The author found it advisable to filter through paper before adding the phenol, to incubate the phenolized emulsion at 37°C. for 48 hours, and to place it in the ice chest for a period. He also suggested the need of further study with regard to various factors in the procedure such as the concentration of virus and of phenol, the length of time, and the best temperature for the action of the phenol, the dosage, and the time necessary for the development of immunity.

Aycock and Kagan (1927, A 44) have reported a small series (4) of monkeys vaccinated with phenolized virus. Suspensions of virulent



cords were made in 1, 0.75, 0.50 and 0.25 per cent phenol and kept in the refrigerator for 7 days. Injections of 8 to 10 cc. (route not stated) were made every second day. Two monkeys developed paralysis during treatment; 1 proved immune; and 1 showed no immunity.

*Formaldehyde.* Unsuccessful attempts to induce immunity with formalin-treated virus have been described by Römer (1913, R 25), by Abramson and Gerber (1918, A 6), and by Jungeblut (personal communication).

*Sodium Ricinoleate.* Experiments suggesting that castor oil attenuates or detoxifies the virus of poliomyelitis were described by McKinley and Larson (1926-1927, M 8), in a preliminary report. Three of 4 monkeys that received an intracerebral or intraperitoneal injection of castor oil soap-virus mixture resisted an intracerebral test inoculation, 10 to 19 days after the immunizing injection. The authors themselves considered the experiment inconclusive because of the small number of animals and also because they were unable to produce the disease with more than 70 to 75 per cent of the inoculations.

*Aluminum Hydroxide.* Artificial immunization by means of virus inactivated by adsorption on particles of aluminum hydroxide has been reported (Rhoads, 1930, 1931, R 8, R 12). Four monkeys were given repeated (5 sets of injections at 3-day intervals, *i.e.*, a total of 75 cc. in 2 weeks) subcutaneous injections of virus (a 10:1 mixture) thus inactivated. One died of intercurrent infection, 3 were tested 1 month later for immunity, first by nasal instillation of glycerolated virus; second, after another interval of 28 days, by intracerebral inoculation of fresh virus. Two of the animals resisted infection, the other developed poliomyelitis as did the control. Neutralizing substances were shown to be present in the blood serum of each of the 3 treated monkeys.

That the virus of poliomyelitis is not destroyed by adsorption on aluminum hydroxide has been shown by Sabin's work on elution (see *Chapter on Etiology*). Thus it may be supposed that immunity produced by this method as well as by others where chemically treated filtrates or emulsions are used is due to the presence of active virus.

*Attenuation by Dilution.* Virulent spinal cord exposed to different glycerol-water dilutions (5 to 50 per cent of glycerol) for 7 months at refrigerator temperature has also been tried as vaccination material (Aycock and Kagan, 1927, A 44). On the assumption that the virus survives only a short time in water (it has, however, been shown to be virulent after preservation in water for 114 days; see under *Properties*

of *Virus*), the lower concentrations were considered less virulent. Eight monkeys were injected subcutaneously, beginning with virus from 5 per cent glycerol and ending with 50 per cent glycerol. Three animals became paralyzed during the vaccinations; 1 died accidentally; 3 proved susceptible to an intracerebral test; 1 resisted.

*Attenuated Strains.* An immunizing strain of the poliomyelitis virus has been described by Flexner and Amoss (1924, F 30) (see *Section on Strains*). Glycerinated brain tissue was received in a slightly putrefactive state; thin sections were placed in phenol for a few hours and then replaced in glycerin; this procedure was repeated once in order to remove contaminating organisms. Monkeys inoculated with this strain showed only mild symptoms, recovered, and later proved immune to a more potent virus (M.A. strain). At the time of writing, this immunizing strain appeared to have a fixed degree of activity; it had neither increased nor decreased in virulence in the 2 years since isolated.

The question whether an attack caused by a weak virus strain may fail to confer immunity against a more potent virus or whether there may be immunological differences between strains of poliomyelitis virus has been discussed by Burnet and Macnamara (1931, B 42) and is taken up more at length under *Strains of Virus*, and under *Specificity of the Reaction of Neutralization*.

**Living Unattenuated Virus.** It is apparent from the preceding that immunization has been obtained, in some instances, with attenuated virus, regardless of the method of modification employed. Aycock and Kagan (1927, A 44) have suggested that the development of immunity may "depend to a certain extent upon the site of inoculation, or the manner of absorption." Thus when vaccination with treated virus meets with success it may be due to the "chance attainment of the necessary conditions in this respect rather than to attenuation of the virus." Many different routes have been employed for the introduction of active virus; the results show that thus far the greatest success has resulted from the intradermal administration of the living agent. Perhaps this is because, as Brodie (personal communication) has suggested, slow absorption of virus is necessary to produce immunity. The uniform failure to obtain immunity by intracerebral inoculation of unmodified virus would be in accord with this supposition.

*Immunization by Subcutaneous Injection.* Flexner and Lewis (F 45; F 46) were the first to confer immunity to monkeys with the untreated poliomyelitis virus. Subcutaneous injection of gradually increasing doses of virus suspension were given over a period of several



months. In certain instances, the animals resisted a full intracerebral injection of the filtrate, given 10 days after the last immunizing dose. Active immunity was also secured by a single large subcutaneous injection of virus emulsion.

This method, however, has not been uniformly successful. Leiner and von Wiesner (1911, Z 3) found their results unsatisfactory. Of 4 monkeys, 1 died of typical poliomyelitis after the fourth injection, 1 developed the marantic type of the disease and 2 died of an intercurrent infection.

The dangers attendant upon such a procedure were also pointed out by Oluf Thomsen (1913, 1914, T 11, T 12). He used gradually increasing doses of a standardized filtrate and gave daily subcutaneous injections for 12 days, but repeated each dose (as Flexner had done) several times before increasing. Later, larger doses were given at weekly intervals. In the first series treated, all the 7 animals showed symptoms such as tremor, excitement, or ataxia and 2 died. But in the second group, also of 7, smaller doses were used and 5 of the monkeys remained entirely without symptoms; 1 showed a slight tremor and 1 developed paralysis of one extremity. All the surviving animals in both groups withstood a subsequent (6 days and 2 months, respectively) intracerebral test.

Virus incorporated in agar and in olive oil has been introduced subcutaneously with partial success (Aycock and Kagan, 1927, A 44). Of 8 monkeys receiving virus in agar, 2 became paralyzed during the course of vaccination, 2 failed to show subsequent immunity, 2 were not tested, and 2 resisted. The one olive oil vaccination was successful.

Experiments on immunization by the subcutaneous route have also been described by Stewart and Rhoads (1929, S 58). As this series was carried out for the purpose of determining whether the subcutaneous or the intradermal introduction of the virus was the more effective, this work is discussed in the next section.

In the 1 monkey treated by this route in a series tested by different methods, Jungeblut and Hazen (1930, J 23) observed no symptoms during treatment but no immunity had developed as shown by the intracerebral test.

### Immunization by Cutaneous or Intracutaneous Methods

*Scarification.* Immunization by rubbing active virus into scarified skin areas was attempted in 1 experiment (A 44). Neither local reaction nor general infection developed in the 2 monkeys treated.

One animal died of an intercurrent infection and the other proved susceptible to an intracerebral test.

*Intracutaneous Injection.* Several sets of experiments have been carried out by this method, with some measure of success. In the first series described (Aycock and Kagan, 1927, A 44), active virus was injected into the skin; 0.05 cc. of a 5 per cent suspension was introduced into each of 20 to 40 piqûres until 1 to 2 cc. was given at each sitting. The total amount given each animal varied from 5 to 76 cc. in 6 to 43 inoculations distributed over a period of 15 days to 5 months. Of 20 monkeys, 1 became paralyzed during treatment; 1 failed to resist intracerebral inoculation; 10 resisted 1 intracerebral test; 2 resisted 2 such tests; and 2 withstood 3 intracerebral inoculations. Serum from 8 of the vaccinated monkeys neutralized virus 21 times. The serum from 1 monkey neutralized virus *in vitro*, although the animal itself did not resist the intracerebral test.

Four monkeys were treated by this route in the comparison of different methods reported by Jungeblut and Hazen (1930, J 23). One developed the disease during treatment; 2 were infected as a result of the intracerebral test; while 1 resisted the first test inoculation but succumbed to the second.

In order to determine the relative efficacy of introducing virus by the intradermal or by the subcutaneous route as a means of producing immunity, Stewart and Rhoads (1929, S 58) carried out 2 series of experiments. Eight monkeys were treated in each group. In the first group, the virus (M.A. or Aycock strain) was given intracutaneously. The injections were made twice a week; 1.5 to 2 cc. of 5 per cent glycerinated virus, distributed in about 20 small blebs was given as a single dosage. The total amount of virus given each animal varied from 42 to 66 cc. over a period of from 3 to 5 months. The course of treatment of the second group was similar but the virus was injected subcutaneously. During the process of immunization, no symptoms were observed that could be interpreted as a mild attack of the disease and thus responsible for the development of immunity. At the end of the immunizing period, serum was obtained from all the monkeys for neutralization tests, before making the intracerebral test inoculation.

The results showed that the degree of immunity produced was much greater in the animals treated by the intradermal method. Although 7 of the 8 monkeys in this series showed slight symptoms following the intracerebral test, no definite paralysis developed in any instance.

On the other hand, 4 of the 8 monkeys immunized by subcutaneous



inoculation of virus developed typical poliomyelitis, although 2 recovered with residual paralysis.

An attempt was made also to detect degrees of immunity by using for the intracerebral inoculation test, not only virus of the strain with which they had been immunized, but also with other strains. Monkeys treated with the M.A. strain were tested with the Aycock virus, and animals immunized with the Aycock strain were tested with the M.A. virus. Emphasis was placed on the difference in the results: monkeys that were resistant to the M.A. virus (a relatively weak strain) were not immune to the stronger Aycock virus. In 3 instances, monkeys that had been immunized with M.A. virus resisted both the M.A. and Aycock strain but 1 developed the typical experimental disease on intracerebral inoculation with an active pooled mixed virus (M.V.)

The results of the serum neutralization tests showed even more strikingly that the immunity induced in monkeys by these methods is one of degree only. Although 4 of the 16 animals developed poliomyelitis as a result of the intracerebral test inoculation, in only one instance did the serum fail to show neutralizing power. Serum from 3 monkeys that showed definite symptoms on intracerebral inoculation, neutralized approximately 50 M.L.D. of an active virus filtrate. Serum from 2 monkeys that had proved susceptible to intracerebral inoculation with the Aycock strain neutralized the active pooled virus. Thus the neutralization test proved more sensitive for the demonstration of immune bodies than direct intracerebral inoculation, in these experiments as well as in those reported by Aycock and Kagan. Stewart and Rhoads suggested that some apparent previous failures in the production of artificial immunity may have been due not so much to the method of immunization employed as to the use of the intracerebral route for the test inoculation.

It has been noted in the preceding paragraphs that, in some instances, monkeys developed paralysis during the process of immunization (Aycock and Kagan, Stewart and Rhoads). However, when relatively weak strains were used, the majority of animals showed no symptoms. In a recent test, Rhoads (1930, R 9) employed repeated intradermal injections of a highly potent virus. Following the third intracutaneous dose, the 4 monkeys, which were being tested, became ataxic, tremulous, and excited. Three recovered while 1 developed paralysis and died. The question was raised as to whether the repeated administration of minute quantities of virus might not leave the animals under treatment more susceptible rather than more resistant to the

virus (see *Allergy*). The effect of a single large dose was, therefore, tried. Four monkeys were each injected intradermally with 16 cc. of a 5 per cent suspension of the pooled, mixed virus strain. This was distributed in small blebs over a large skin area. No local reaction and no symptoms of poliomyelitis were observed. A month later, serum was obtained from each monkey and a test inoculation by the cisternal route was performed (only 3 animals could be used for the test inoculation as 1 died of an intercurrent infection). Serum neutralization was complete in every case. Of the 3 monkeys inoculated intracisterally, 2 remained free of all symptoms, 1 developed the experimental disease but recovered with a marked residual paralysis. As a rule, an inoculation with this strain is followed by death.

See later paragraphs for administration of serum-virus mixtures by subcutaneous and intradermal routes.

*Immunization by the Intracerebral Route.* Early in the course of experimental work it was observed "that failure to develop paralyzes after an intracerebral inoculation of an active virus does not lead to any increase in resistance of the monkeys to subsequent infection by the same route" (Flexner and Lewis, eighth note, 1910, F 46). This fact is so generally accepted now that it is customary to use such animals for controls in later experiments. Further justification for this practice may be found in certain experiments described by Brodie (personal communication) in which gradually increasing quantities of virus were injected intracerebrally in order to determine the minimal infective dose. The difference between the last two amounts was so small that it was evident that no immunity had developed or infection would not have resulted from so slight an increase; moreover, other animals that had not received the preliminary series of inoculations were completely paralyzed by the same final dose but not by the one just preceding.

*Immunization by the Gastro-intestinal Route.* Although only one experiment (see below) has been carried out with a view to inducing immunity by the gastro-intestinal administration of virus, in some cases tests for immunity have been made following attempts to produce infection by this route (see under *Routes of Inoculation*). In most instances no immunity was demonstrated (Landsteiner and Levaditi, L 5, L 46, L 6, L 34; Amoss, 1928, A 18; Schultz, 1929, S 12; Kling, Levaditi, and Lépine, 1929, K 13; Levaditi, Kling, and Lépine, 1931, L 43). In 2 experiments reported, however, it seemed possible that partial immunity had been developed. In the instance reported by Leake (1918, L 18), 1 of the 2 monkeys that had received virus mixed with food survived



intracerebral inoculation 104 days later but succumbed to a second injection 48 days after the first. Thompson (1930, T 8) reported inconclusive immunity tests following gastro-intestinal administration of virus. Two monkeys resisted 1 intracerebral test; 1 of those withstood a second inoculation, but showed a delayed weakness of the legs; a third animal developed poliomyelitis following the first test injection but in extremely mild form.

After cleansing the colon, 2 monkeys were given 4 intrarectal injections of virus, in an attempt to induce active immunity (Jungeblut and Hazen, 1930, J 23). Neither animal withstood a subsequent intracerebral test.

*Immunization by Intrasplenic Injections.* Only an incomplete report of the work done by Brebner (1931, B 27) has been published (see *Anaphylactic Reactions Produced by Intrasplenic Injection under Allergy*). Humoral neutralizing antibodies were produced in 15 monkeys by the injection of many infective doses of virus directly into the spleen. The author has stressed the importance of "placing" a virus antigen. The possible association of the spleen and the reticulo-endothelial system with the production of antibodies has, perhaps, received too little attention in the study of poliomyelitis.

*Immunization by Miscellaneous Routes.* Immunity resulting from repeated *intraperitoneal* injections has been described by Pettit (1929, 1931, P 16, P 17). The serum obtained showed neutralizing power *in vitro* and was also reported to be effective in the treatment of the human as well as of the experimental disease. Further mention of this serum is found under *Immune Sera*.

On the other hand, Jungeblut and Hazen (1930, J 23) found that the 2 animals that had received virus *intraperitoneally* were not immune to a test inoculation. In another experiment a collodion sac, containing 3 cc. of virus suspension, was placed in the peritoneal cavity of each of 4 monkeys and left there indefinitely; 1 withstood 1 intracerebral injection of virus but succumbed to the second. Another group of 6 monkeys, similarly treated, died with cachexia in 2 to 4 weeks. Slight motor symptoms were observed but no histological evidence of poliomyelitis was found.

In the course of experiments designed to show whether the virus of poliomyelitis can survive in the monkey testicle (Jungeblut and Thompson, 1930, J 29) it was observed that no immunity had been induced either in the *testicle-inoculated* monkeys or in the animals that were injected intracerebrally with testicular emulsions.

Two of 3 monkeys that received 3 *intrapleural* injections each (Jungeblut and Hazen, 1930, J 23) resisted 1 intracerebral inoculation; 1 was re-tested a month later and succumbed.

In a later report (1931, J 24) these authors described an attempt to induce active immunity in 4 monkeys by repeated *spraying of the nose and throat* with a virus emulsion. Treatments were given twice a week over a period of about 10 weeks. One animal died of an intercurrent infection. The other 3 failed to resist an intracerebral test and their serum (0.5 cc.) failed to neutralize 0.5 cc. of a 1 per cent virus emulsion.

**Immunization with Combinations of Virus and Immune Serum.** Active immunization has also been attempted by the administration of various types of immune serum and virus, either in the form of neutralized mixtures or separately. Since different workers have used immune serum from a variety of sources and virus of varying potency, and have injected these materials by various routes, comparison of their results is difficult and cannot lead to very definite conclusions.

**Serum-virus Mixtures, with Human or Monkey Serum.** In 1910, Römer and Joseph (R 26, R 27) reported that 4 monkeys each of which had received an intracerebral injection of a mixture of virus and human convalescent serum, had survived an inoculation which produced paralysis in the controls. In the same year, Flexner and Lewis (1910, eighth note, F 46) stated that neutralized mixtures of virus and immune serum did not induce active immunity (route not stated; the inference from context is that injections were intracerebral). Römer (1913, R 25) later attributed his success to the fact that he had used serum from convalescent human cases containing only a small quantity of antibody, whereas Flexner and Lewis had used serum from highly immunized monkeys.

In the 1 monkey treated, Thompson (1930, T 8) obtained no evidence of immunity by the intracerebral test 10 weeks after a series of injections (1 intracerebral and 4 subcutaneous) of a mixture of convalescent monkey serum and virus distributed over a period of 30 days.

A mixture of virus and immune serum was used in 1 of a group of experiments reported by Goldbloom, Brodie and Moffatt (1930, G 12) in an effort to repeat the work of Römer and Joseph. The mixtures were given twice a week for 3 weeks. Two of the 5 monkeys used died of tuberculosis during the course of treatment; the other 3 failed to resist the intracerebral test inoculation.

Thus no one that has used monkey serum has been able to confirm Römer's results with a mixture of virus and human serum, inoculated



intracerebrally. Morgan and Fairbrother (1930, M 46) have commented that "it has been shown repeatedly that no immunity follows the intracerebral inoculation of serum-virus mixtures into monkeys."

Three routes of administration—intradermal, subcutaneous, and intranasal—were tried out in a series of experiments reported by Rhoads (1931, R 11). Human convalescent serum of suitable inactivating power and a highly potent virus strain were used. The results suggested that, in certain animals, immunity may be induced by the injection of neutralized virus. Intranasal instillation of 30 cc. of a serum-virus mixture over a period of 2 weeks afforded protection to only 1 of 4 monkeys against the subsequent intranasal inoculation of a potent virus. But when the intradermal and subcutaneous routes were used, a greater degree of protection was induced. One-half (6 out of 12) of the animals tested resisted intracisternal or intranasal (2 sets of instillations) inoculation of an active virus; and serum from 5 of the 6 monkeys was effective in neutralizing a potent virus. None of the monkeys showed symptoms during the course of treatment. Rhoads felt that a satisfactory explanation of the superiority of the intradermal and subcutaneous routes over the intranasal could not be given but suggested that the fact that neutralizing substances are present in the nasal mucosa of normal adults might have some bearing on the subject.

**Serum-virus Mixtures with Sheep or Horse Antipoliomyelitic Serum.** In a few instances, attempts have been made to induce immunity in monkeys by the administration of virus and serum from immunized refractory animals. Levaditi and Landsteiner (1910, L 46) used a mixture of virus and the serum from a sheep that had received subcutaneous inoculations of a virulent emulsion; the treated monkey was given 2 injections of this mixture subcutaneously and resisted a test inoculation (route not stated) 11 days and again 23 days following the second treatment.

Repeated sets of intradermal injections of virus neutralized by globulin fractionated horse antipoliomyelitic serum produced immunity in one-half of the monkeys treated (Rhoads, 1931, R 11). Two animals showed no evidence of infection, 1 showed slight symptoms, and 1 succumbed as the result of the nasal instillation of virus a month later. The 3 surviving animals withstood a subsequent intracerebral test.

**Administration of Virus and Immune Serum Uncombined.** It was observed by Andrewes (1928, cited by Rhoads, R 11; Andrewes,

A 29) that immunity had developed in part of a group of rabbits that had received an intravenous injection of vaccine virus in one ear and, at the same time, an injection of immune serum in the other ear.

Success in inducing active immunity against poliomyelitis when virus and serum were given separately either at the same, or at different times, has been reported by Goldbloom, Brodie and Moffatt (1930, G 12) and Brodie and Goldbloom (1931, B 32). Serum, mixed with virus, was found to have an inhibitory action on antigenesis. Since attempts to attenuate or otherwise alter virus outside the body also affected its antigenic powers, the authors used, in their first experiments, brain tissue which in itself, did not contain sufficient virus to produce poliomyelitis on intracerebral injection. Five monkeys were used; a different quantity of a 5 per cent suspension was injected intradermally into each animal. Immune serum, also in varying dosages, was injected intracutaneously or intramuscularly either simultaneously with, or following, the administration of virus. By the neutralization test, it was shown that immunity had been produced in 2 of the 5 animals. The authors concluded that the serum should be given only after the virus had acted alone for 1 or 2 days and that a single large dose was preferable to small or repeated smaller doses.

In their next series of experiments, active cord virus was used throughout ("Fl mixed virus") and the potency was checked at intervals; the virus was injected intradermally in one piqure though some infiltration into the subcutaneous tissues probably took place. Pooled human convalescent serum of tested neutralizing power was given subcutaneously. In the first experiment, each of 5 monkeys received the equivalent of 20 to 30 cc. of a 5 per cent emulsion in 1 or 2 injections, and 5 to 10 cc. of serum, also in 1 or 2 injections, either with, or subsequent to, the virus. Sera from 4 of the 5 animals neutralized 0.05 cc. of a 5 per cent active cord emulsion but the 3 sera tested failed to neutralize 0.1 cc.

In the next experiments, a fixed quantity of virus (1 gram of spinal cord, or 20 cc. of a 5 per cent suspension) was used but the dose and times of administration of the immune serum were varied. It was found that 6 cc. of serum subcutaneously protected against the above quantity of virus when administered intradermally simultaneously with, 3 days after, or 3 days preceding, the virus injection. But when the virus was given subcutaneously and the serum intradermally, infection resulted.

Neutralization tests carried out 5 weeks after the course of vaccina-



tion had been completed, indicated that when the immune serum was given with or after the virus injection, a greater degree of immunity was induced, than when the serum was given first; and that, under the conditions described, this immunity was sufficient to afford resistance to  $2\frac{1}{2}$  times the dose of virus that produced paralysis in controls.

In the above experiments, immunization was carried out in 8 animals (with 1 gram of virus and 6 cc. of immune serum). Six of these withstood an injection (route not stated) of 0.05 cc. of a 5 per cent virus emulsion, 0.01 cc. of which had been shown to produce infection; and 2 developed partial immunity as shown by a prolonged incubation period and a milder illness. Brodie and Goldbloom comment that, with larger amounts of virus, Rhoads (1931, R 11) did not obtain as complete immunity, employing a serum-virus mixture, with more serum in proportion to virus than was used in the work just described. Reference is made to the fact that neutralization of the virus with immune serum does not destroy the virus, but Brodie and Goldbloom suggest that a mixture of virus and serum may not dissociate sufficiently in the body to immunize efficiently, and that immunity may be induced only when the serum is not in excess.

Since the publication of the above articles, Brodie (1932, B 31) tested another series of 9 animals (3 died of an intercurrent infection). A single dose of 1.5 grams of virus and 9 cc. of serum was administered. Again, it was found that, when the injection of serum preceded the virus inoculation, immunity was less than when both were given simultaneously or when the serum followed the virus. Immunity for the group lay between 2 and 5 M.L.D. Thus the results were poorer than in the series described above. The animals used proved to be equally susceptible and the immune serum had less neutralizing power. The virus, however, was weaker. Tests showed that there was a relationship between the strength of virus and the amount of immunity induced.

A series of experiments was then carried out, using virus attenuated by taking cord at different intervals after paralysis. When the virus was one-eightieth as strong as whole cord virus (6 days after paralysis), sufficient immunity was induced to neutralize between 1 and 2 lethal doses. With virus taken at shorter intervals, a greater degree of immunity developed. Then brain tissue alone was used. A small amount of immunity resulted from the injection of virus taken from the motor cortex. Brodie concluded, therefore, that immunity is proportional to the infectivity of the virus.

## IMMUNE SERA

The presence or absence of neutralizing substances in sera from various sources has been of interest, not only as an indication of the distribution of immunity to poliomyelitis but because of the use of immune sera in experimental work and in attempts to combat the human disease. For these purposes, a serum with a high degree of neutralizing power is important. Efforts have, therefore, been made to determine the effectiveness of the human sera obtained from different groups of donors and also to produce a potent animal serum that could be secured in large quantities. Although these experiments have been carried out with a number of different virus strains, the results are doubtless comparable since Weyer, Park and Banzhaf (1931, W 17) have noted that "the potency of the virus has apparently no effect upon the amount of a specified serum preparation needed to neutralize it. When using particularly potent strains of virus the inoculum often contains as many as several hundred killing doses of virus."

### Human Immune Serum

*Antibody Content of Normal and Convalescent Serum.* It has already been noted that "normal" human serum may have neutralizing power and that convalescent serum occasionally fails to exhibit this property. In the treatment of 156 acute cases of poliomyelitis, Zingher (1917, Z 5) obtained nearly the same results with normal as with convalescent serum, although no tests for potency were made. In a small series of cases, Fairbrother and Brown (1930, F 5) found that the sera both of normal contacts and of convalescents (all children) had neutralizing power although they were unable to compare the degree of protection afforded by sera from these two groups.

Normal and convalescent sera have, however, been compared quantitatively in *in vitro* tests by Shaughnessy, Harmon and Gordon (1930, S 33). The results showed that serum from persons who had been in contact with poliomyelitis cases possessed neutralizing power equal to or greater than that shown by the serum of recovered persons. Serum from normal adults, who had had no known contact with the disease, was equal in potency to that from contacts and was, apparently, more potent than sera from convalescents. Moreover, 3 of 14 specimens of convalescent serum failed to neutralize in any dilution. Thus neutralization tests suggested that the immunity acquired by a normal person may be greater than the immunity following an attack of the disease.

A high degree of immunity may even be developed early in life; the



serum from a supposedly normal child of 8 years was found by Rhoads (1931, R 13) to have a neutralizing value about equal to that of a pooled human convalescent serum and of a pooled reinforced monkey serum.

Schultz and Gebhardt (1931, S 14) have tested quantitatively the neutralizing power of the sera of 32 "normal" adults. In one series of 13, in which the serum-virus mixtures were incubated 2 hours before injection, 9 inactivated the virus in a dilution of 1:2. In a second series of 19, not incubated, 9 inactivated the virus in a dilution of 1:60. These authors also suggested that "the incidence of persons whose serum will titer as high, or higher, than the average convalescent serum . . . may be of fair magnitude." Of 4 convalescent sera tested, only 2 neutralized in a dilution of 1:2.

The effectiveness of normal human serum has likewise been noted by Weyer, Park and Banzhaf (1931, W 17). Titration of 2 samples of pooled convalescent serum (each sample contained serum from 16 individuals) showed that such serum regularly neutralized 5 per cent virus emulsion in a ratio of 1:20, but failed in 1:30. Four out of 9 individual sera from normal adults were effective in a ratio of 1:10, and 1 other neutralized in a ratio of 1:14.

Hudson and Lennette (1932, H 38 a) have recently examined the neutralizing effect of pooled human serum on the poliomyelitis virus. "Ten specimens of pooled serum from city-dwelling adults and from persons of various ages convalescent from poliomyelitis were tested. . . . The number of individuals contributing to the pools varied from 5 to 50. All specimens manifested neutralizing properties when the serum was undiluted and frequently when examined in dilutions of 1:5 and 1:25. This type of biological technic does not allow for exactitude in interpreting comparative titers when the differences are so small as were demonstrated by the two types of serum in these experiments."

In coöperation with the State Department of Public Health of Tennessee, Hudson and Litterer (personal communication) "examined the serum of 25 'normal' adults of Nashville and found that 21 neutralized the virus when the serum was undiluted. These 21 specimens were then tested in a dilution of 1:5 and 16 of them neutralized the virus."

In comparing the antibody content of normal serum with that of convalescent serum, it has been observed that the latter may vary in strength (Brodie, 1932, B 30, B 31, personal communication). Pooled sera from 4 groups of donors differed considerably in antibody titer; the weakest showed only 58 per cent of the neutralizing power of the strongest. The protective power of the sera from 29 "normal"

urban adults was compared with the average protective power of the 4 samples of pooled convalescent serum. Fourteen were low in neutralizing power, four-fifths or more of the strength of this standard; and 6 of 8 that were re-tested were equal in titer to the average convalescent serum.

While making a study of the blood grouping of acute and convalescent cases, Jungeblut and Smith (1932, J 27) found that 6 out of 7 group B sera were effective in neutralization tests but only about half of the 19 sera belonging to blood groups O, A, and AB had protective power. These results suggest that determination of the blood grouping might afford a means by which suitable donors of a potent convalescent serum could be selected.

**Relative Potency of Serum from Recent Cases and from Cases of Long Standing.** Sera from a small group of persons recently convalescent (up to 1 year) were compared in neutralizing power with sera from persons infected 3 years previously (Burnet and Macnamara, 1929, B 41). No significant difference in virucidal properties was detected, although the serum from the older cases seemed slightly more potent. Judging from another small series described by Shaughnessy, Harmon and Gordon (1930, S 33), sera from cases of long standing ("three to seven years," or "more than ten years before the test") was slightly more effective than sera from cases that had had poliomyelitis 6 months to 2 years before the test.

**Effect of Storage on the Potency of Serum.** Burnet and Macnamara (1929, B 41) tested the activity of convalescent serum, prepared from oxalated plasma, filtered, sealed in ampoules without added antiseptic, and stored for 3 years at ice-box temperature. The stored sera protected monkeys against both a local (Australian) virus and a virulent American strain although it seemed to have slightly less protective power than serum from the same persons but prepared within a year. It would have been interesting if, in this experiment, the titer of the serum before and after storage could have been determined and if the original titer could have been compared with that of the serum of the same persons after the 3-year interval.

Although no tests were described that would show whether any deterioration had taken place, Brodie (1932, B 31) noted that a specimen of pooled convalescent serum, 2 years old, was more highly protective than 3 samples that were collected in 1931. This raises other questions with regard to the cause of variations in the strength of sera.

**Selection of a Potent Serum.** The therapeutic and prophylactic



value of human immune serum is discussed in the *Chapter on Treatment* and will not be entered into here. But if human sera of high antibody content are to be used on a large scale for any purpose, every means that will assist in the selection of such a serum must be employed, as it is obviously impossible to test each sample for neutralizing power. It has already been mentioned in this chapter (see also under *The Host, Chapter on Epidemiology*) that Grooten and Kossovitch (1930, G 18), Foà (1931, F 55), and Jungeblut and Smith (1932, J 27) have found that individuals belonging to blood group B are on the average more resistant to poliomyelitis than those of other groups, since a smaller percentage of this group develop the disease. Serum from group B donors has proved in a few instances more effective in neutralization tests, than serum from donors of other groups.

The optimum time for collecting serum has not been determined. As noted earlier in this chapter, neutralizing substances have been detected in the blood early in the course of the disease: on the third day of illness in a human case (Kling and Levaditi); 36 hours after the onset of paralysis in the experimental disease (Brodie). In a number of cases tested at the Research Laboratory, the antibody first appeared some weeks after convalescence (personal communication from Dr. Park). Aycock and Kramer (1930, A 46) have recorded an instance in which specimens of monkey serum taken 3 and 6 weeks after the disease, failed to neutralize virus, but serum from the same animal taken 6 months after convalescence effected neutralization. Further experimental data are needed as to the period after the disease when the neutralizing power of the serum has reached its height.

**Preparation of the Serum.** No attempt will be made here to describe the technic of preparing the serum as it differs in no essential features from that used in obtaining convalescent sera in other diseases; one point, though, may be mentioned. In the United States, preservative is usually added; Macnamara and Morgan (1932, M 12) have, however, employed in Australia a serum that is free from hemolysis and from added antiseptic and from which the fibrinogen has been removed as completely as possible. The authors believe that such serum is less likely to produce unpleasant reactions.

### Monkey Immune Serum

*Normal and Convalescent Monkey Serum.* As previously mentioned, normal monkey serum from young monkeys is apparently entirely lacking in neutralizing power while, with few exceptions, con-

valescent monkey serum exhibits this property, though in variable degree. Leake (1918, L 18) and Aycock and Kramer (1930, A 46) mention certain failures with convalescent monkey serum, but, in those instances in which re-tests were made, serum from the same animal neutralized virus on one or more occasions.

*Serum of Actively Immunized Monkeys.* It has already been noted that the demonstration of neutralizing substances in the serum is a more delicate test for immunity than resistance to intracerebral inoculation. The results obtained as the consequence of immunizing procedures have been described in the *Section on Active Immunization*. In only two instances has there been an attempt to produce a therapeutic serum in monkeys (Pettit, 1929, 1931, P 16, P 17). The *Cynocephalus hamadryas*, weight 15 to 20 kgm., was chosen as the most promising species available. Immunization was easily accomplished; after a preliminary injection of a mixture of virus and horse or monkey anti-poliomyelitis serum, 2 to 4 intraperitoneal or subcutaneous injections were given at weekly intervals. Bleedings were made 2 to 3 weeks after the last injection; the optimum interval had not been determined; 0.5 cc. of serum neutralized 1 cc. of cord emulsion, and was apparently more potent than their horse serum although accurate comparisons had not been possible because of an insufficient supply of monkeys.

More recently, Pettit, Erber, and Kolochine (1932, P 18) were able to carry out a similar course of immunization with a chimpanzee, an adult female, weighing about 30 kgm. Serum withdrawn before the treatment did not neutralize virus even in the ratio of 1 cc. of serum to 0.2 cc. of emulsion, but on the fifteenth day after the second injection, neutralizing properties had developed. According to this group of workers, the advantages of using a chimpanzee are: a larger quantity of serum can be obtained than from smaller animals; the elaboration of immune bodies proceeds more rapidly and reaches a higher titer; and, moreover, the serum of the anthropoids is tolerated perfectly by the human organism.

**Hyperimmune Monkey Serum.** In order to obtain an effective serum for neutralization tests and other experimental work, Flexner and Lewis (1910, F 46), Flexner (1910, F 11), and others have frequently attempted to "re-inforce" the immunity of convalescent monkeys by repeated inoculations of virulent material. In this way, sera of high titer (1:128, Schultz and Gebhardt, 1931, S 15) have been obtained.

That the inactivating power of serum is definitely raised by "re-inforcement" has recently been shown by Rhoads (1931, R 13).



Pooled serum from a group of 6 monkeys with residual paralysis did not neutralize 0.12 cc. of a potent virus filtrate in quantities less than 0.75 to 1 cc. A sample of pooled human convalescent serum, and also a specimen of serum from a "normal" child of 8 years were each effective in a volume of 0.1 cc. against the same quantity of virus. Pooled serum from the same group of monkeys, taken after a series of intradermal injections, was equal in neutralizing value to that of the human pooled convalescent serum.

### Serum of Animals Refractory to Poliomyelitis

**Small Laboratory Animals.** Reference to the possibility of the development of neutralizing substances in the serum of the smaller refractory animals is made in the section dealing with efforts to transmit the disease to animals other than the monkey (see *Chapter on Etiology*).

**Sheep and Horses.** Although the experimental disease has, thus far, been transmitted with certainty, only to monkeys, many attempts have been made to produce in larger animals, as sheep and horses, an immune serum that could be used therapeutically either for passive immunization or for active treatment. The clinical evidence for, or against, the use of these sera in the control of the human disease is discussed in the *Chapter on Treatment*. Only the experimental work on the subject will be considered here.

Early in the history of the experimental disease, Flexner and Lewis (1910, F 45; Flexner, 1910, F 11) reported that they had been unable to produce a neutralizing serum in a horse in spite of repeated injections of an active virus filtrate over a period of many months. The serum did not neutralize *in vitro* and was, moreover, without preventive action when injected subdurally 18 to 24 hours after an intracerebral injection of virus, although convalescent monkey serum did protect when thus injected. It was found that normal sheep serum had neutralizing power and that this property could be increased by the injection of a virulent emulsion. A later statement (Flexner and Stewart, 1928, F 54), however, was made to the effect that repeated injections of virus do not increase the natural inhibiting effect present in certain animals.

Kraus (1911, K 27) obtained a virucidal serum by giving a sheep subcutaneous injections of a virus emulsion over a period of 5 months. The serum then neutralized virus *in vitro* though normal sheep serum did not. But intraperitoneal injection of 10 cc. of the neutralizing serum did not protect a monkey against a subdural injection of virus

24 or 40 hours later. He felt that this excluded the possibility of using the serum for curative purposes.

By both subcutaneous and intramuscular inoculation of increasing doses of a filtrate of human brain and cord emulsion, Neustaedter and Banzhaf (1917, N 14) obtained a horse serum of definite neutralizing value. Intramuscular injection of this serum 24 hours after the intraspinal injection of virus protected 1 monkey against infection; but, when given 48 hours after the virus inoculation, no protection was afforded.

On the other hand, Leake (1918, L 18), and Dixon and Rucker (1918, D 15) failed to find evidence of antiviral substances in the serum of horses that had received immunizing treatment.

A neutralizing sheep serum was obtained by Pettit (1918, P 14) after the administration of a series of intravenous injections of a virulent emulsion. Later, the sheep serum was abandoned on account of serum accidents and a horse serum was prepared at the Pasteur Institute by the same method (Stefanopoulo, 1924, S 55; Pettit, 1925, P 15; Pettit, 1931, P 17). Unfortunately, because of an inadequate supply of monkeys, very few neutralization tests could be carried out; only one such experiment was described; nor was any preliminary determination of neutralizing power made before the course of injections was begun. Stefanopoulo felt, moreover, that clinical efficacy was a better indication of the value of the serum than laboratory tests and evidently placed reliance on the reported success of the use of the serum in the treatment of the human disease.

Neutralization tests with the Pettit horse serum have been carried out, however, by Stewart and Haselbauer (1928, S 56). Of 6 monkeys inoculated with a mixture of this serum and virus, only 1 remained well, 3 developed typical poliomyelitis, and 2 were described as having a questionable attack of the disease. Two tests were made also with "immune" sheep sera prepared by the authors according to Pettit's method. Although serum from the 2 animals in question neutralized virus *in vitro* before the course of immunizing injections had been given, serum obtained after treatment showed no neutralizing power. The authors felt that "the reason for such chance neutralization is obscure and should not be confused with the constant virus-neutralizing action of both human and monkey convalescent sera."

The most extensive work in the production of an antipoliomyelitic horse serum has been carried out by Weyer, Park, and Banzhaf (1929, 1931, W 16a, W 17). In the first report (read before the American Association of Pathologists and Bacteriologists, March 26, 1929), an



account was given of 3 horses subjected to immunizing treatment over periods ranging from 4 or 5 months to 2 years. One of the 3 horses produced a highly potent serum. In the following 2 years 8 more horses were injected. Four produced potent serum. The sequence of the injections was varied and so was the route of inoculation; injections were made subcutaneously, intradermally, intramuscularly, and intravenously. Three of the animals failed to respond with the development of antibody and were abandoned, 1 after a period of 3 months and 2 after a year's treatment. In 3 instances (Horses 4, 7 and 8) the antibody content of the sera rose to a titer of 25:1; Horses 7 and 8 had been treated for a period of only 5 months; during part of this time, 0.1 per cent of alum had been added to the saline with which the emulsions were prepared.

Citrated solutions of bleedings from Horses 4, 9 and 10 were concentrated by Banzhaf's method of fractional concentration of antisera with ammonium sulphate (Banzhaf 1912-1913, B 4), without the heating process. As a result of this procedure, the globulin (pseudoglobulin) concentration was increased 3 or 4 fold, but with an antibody loss of about 50 per cent. Although the average normal adult serum was effective only in a ratio of 1:10 and pooled convalescent serum in 1:20, concentrated preparations from 2 of the animals (horses) neutralized virus in a ratio of 1:100.

By continuing the injection of the horses (Weyer, 1931, W 16) and also the passage of the virus through monkeys, a serum was obtained which neutralized monkey virus in a dilution of 1:500. But in spite of the high neutralizing power of the horse concentrate for the monkey virus, human strains recently isolated (during the 1931 epidemic) were not neutralized in a dilution of 1:20; convalescent serum from previous epidemics, however, neutralized the recent human strains in dilutions up to 1:50. This alteration in the monkey virus suggested the need of using human virus for the injection of horses or a human virus which has passed through only a small series of monkeys (see *Strains of Virus, Chapter II*).

The efficacy of the serum concentrate as compared with that of human convalescent serum in the treatment of the experimental disease was tested by intravenous and intraspinal injection at different intervals subsequent to the intranasal administration of a potent virus strain. Only 1 of 4 monkeys that received the human serum intraspinally, 3 or 5 days after the nasal inoculation was completed, survived; 4 of the 6 treated with horse globulin intravenously in 1 or 2 injections

survived, but 8 out of the 9 animals treated with horse globulin intraspinally failed to develop the disease although, in 2 instances, the interval after inoculation was longer.

Prophylactic treatment too was apparently successful in the few experiments tried. Horse serum concentrate (10 cc.) seemingly afforded protection against intranasal inoculation for 5 weeks although human convalescent serum (20 cc.) failed to protect for 3 weeks. (For discussion of the human disease, see *Chapter V*.) But when the injection was made intracerebrally, a large dose of serum given at the same time failed to protect. Thus, as Dr. Park has said, when the nervous system is infected, it is too late for the antiserum to have any effect.

The horse antipoliomyelitic serum prepared by the above authors was further studied for its antiviral effects both *in vitro* and *in vivo* by Rhoads (1931, R 10). The preparation was tested in 3 forms: citrated blood plasma, serum, and globulin concentrate. An active virus filtrate, M.V., was employed. The tests made were regarded as confirmatory of the presence of inactivating substances that were effective *in vitro*. That precipitin was not an important factor in the inactivation was indicated by the 1 absorption experiment performed; in this experiment the inactivating substances in the horse globulin were not removed by absorption with normal monkey brain.

Prophylactic and therapeutic tests, however, as carried out by Rhoads, suggested that horse globulin was less effective than human or monkey convalescent serum. Although 2 cc. of one of these sera, injected intrathecally, protected against an intracerebral injection of virus given 4 days later, the antipoliomyelitic horse globulin solution had no restraining effect. When the globulin was given intraspinally 3 days after the nasal administration of virus, 1 of 3 monkeys showed no symptoms, 1 had mild symptoms (excitement, ruffled fur), and 1 died of typical poliomyelitis. Antidiphtheria globulin, used for control, apparently protected the 2 animals to which it was given. Rhoads suggested that the marked potency of the virus strain employed might account for the difference in the degree of protection afforded in the experiments just referred to and those described by Weyer, Park and Banzhaf. The immunological differences between these strains passed through a long series of monkeys and other strains may account in some degree for the difference in effect.

Several varieties of refractory animals—the guinea pig, rabbit, dog, sheep, goat, and horse—have been studied by Schultz and Gebhardt (1930, 1931, S 16, S 15), for their capacity to produce an antiviral



serum. Various routes were used for the injection of the virus, which was administered at short intervals for varying periods, a few months for the smaller animals, with longer periods (8 months to 1 year) for the larger ones (horse and sheep). The neutralization tests were carried out in the customary manner except that virus suspensions and immune serum were used in equal volumes instead of the usual 1:9 ratio. In certain of the tests, when undiluted immune serum (rabbit, sheep) was used, neutralization was effected, "*but on diluting these sera, even to a dilution of 1:2 (after addition of virus suspension 1:4) no viricidal action was realized with any of these sera.*"

More satisfactory results were, however, obtained with the horse. After a period of 8 months of immunizing treatment (intravenous injections), the serum inactivated an equal volume of a 5 per cent virus suspension in a final dilution of 1:60. The authors had obtained a higher titer (1:128) with some hyperimmunized poliomyelitis convalescent monkey sera but believed that further treatment might raise the antibody content of the horse serum.

Fairbrother and Morgan (1930, 1931, F 4, F 7, M 46, F 8) obtained antiviral sera from 2 of 4 horses subjected to immunizing treatment. None of the sera showed neutralizing properties before immunization. Both the intramuscular and the intravenous routes were used for the injection of an active virus filtrate. In 2 instances an unfiltered emulsion was used for the preliminary inoculations but was discontinued because of the severe anaphylactic shock which resulted. The results of some of the experiments recorded in the first paper were difficult to evaluate because of an intestinal infection in the experimental animals but it was shown that the serum obtained at the end of the course of injections had a higher antiviral content than samples that were taken earlier. Although only a few samples of human convalescent sera were tested, their neutralizing power was no greater than the third bleeding from the horse in question (Horse 1). After the injections were discontinued, the neutralizing power of the serum diminished rapidly. It may be noted here that the interval between an injection and the subsequent bleeding was in most instances short (4 to 7 days). The few curative tests attempted were not satisfactory. The serum from the fourth horse (Horse 4) (F 8) proved to be extremely rich in antiviral content; 0.005 cc. completely neutralized 0.2 cc. virus, which was estimated as 100 minimal infective doses.

A study was then made of the concentrated serum and the distribution of the antiviral body in the various protein fractions. The authors comment that "while the antitoxins are mainly associated with

the serum pseudoglobulin, the immune bodies which make up the antibacterial or antiviral components of an immune serum are largely precipitated with a water-insoluble serum globulin." Although Weyer, Park, and Banzhaf had found that the poliomyelitis antibody was associated with the serum pseudoglobulin, Fairbrother and Morgan concluded that the antiviral body was distributed throughout the serum but that it was found in different amounts in the various protein fractions. They explained the loss of antibody by concentration, noted by Weyer, Park, and Banzhaf, on the ground that the protective substance does not appear to be concentrated entirely in any one of the serum proteins. In the case of Horse 1 (M 46) approximately 0.13 mgm. of the serum euglobulin effected complete neutralization, but 10 or 15 times as much of the reconcentrated pseudoglobulin or albumin was required for the same purpose. A similar distribution was demonstrated in the serum of Horse 4 (F 8). In this instance, 0.017 mgm. of the euglobulin portion neutralized a test dose of virus, while 0.23 and 0.49 mgm. of the pseudoglobulin and albumin fractions, respectively, was required. The authors felt, therefore, that a highly concentrated antiviral preparation could be obtained by collecting the "euglobulin" fraction and dissolving it in saline.

After a prolonged period of immunization (16 and 20 months for the goats and 2 years for the sheep), antiviral properties were demonstrated in the serum of 2 goats and a sheep (Howitt, Shaw, Thelander, and Limper, 1931, H 37; Howitt, 1932, H 35). Neutralization tests had shown that such properties were absent before treatment. Injections of virus were made by different routes, intravenous, intramuscular, and subcutaneous; the titer rose more rapidly when the inoculations were made intramuscularly and subcutaneously than when they were given intravenously. The sheep responded less readily than the goats. During the later stages of the immunizing course, sera of both goats and the sheep serum had reached as high or a higher degree of potency than that reported elsewhere for immune horse serum (Fairbrother, F 4).

The potency of these sera was also tested by a variety of *in vivo* experiments. Intrathecal injections of the goat sera protected monkeys against intravenous inoculations of virus. Serum obtained from the sheep, late in the immunizing period, showed greater protective power than it had earlier. Three intramuscular injections of serum apparently protected against intranasal instillations of active virus; one-half of the same monkeys were protected against an intracranial inoculation of a weak virus. When the serum was given either intra-



venously or intramuscularly before an intracranial injection of virus, protection was afforded. Both the goat and sheep sera were used in the treatment of a small series of human cases (see first report, H 37; see also *Chapter on Treatment*) and the results were considered encouraging.

#### Specific Nature of the Antiviral Substance in Horse Serum.

The question has been raised as to whether the mechanism of inactivation which occurs with horse or sheep antipoliomyelitic serum is identical with that which takes place with immune human or monkey serum. As previously noted the results of *in vivo* tests described by Rhoads (1931, R 10) showed that the antipoliomyelitic horse serum was irregular in its action. This was contrasted with the constancy of the results obtained with convalescent human and monkey sera. After filtration through Berkefeld candles, the horse globulin concentrate was found to have lost its neutralizing power. Filtration has no effect on the potency of convalescent sera although no tests have been made with globulin concentrates of these sera.

Evidence of the specific nature of the neutralizing substances in the serum fractions of the horse serum is afforded by the control tests described by Morgan and Fairbrother (1930, M 46). The pseudoglobulin fraction of reconcentrated diphtheria and tetanus antitoxins and the euglobulin fraction of a commercial sample of Rosenow's concentrated antipoliomyelitis serum were lacking in protective power even when comparatively large amounts were used.

The possible nonspecific character of the phenomenon has been discussed by Weyer, Park, and Banzhaf (1931, W 17). The immunizing material injected necessarily contains nerve tissue, which results in the formation of anti-substances as shown by complement-fixation or flocculation tests. But, it is argued, it is improbable that this flocculation effects the inactivation of the virus by entrainment since it has been shown that the serum is potent even after the antinerve tissue substances have been removed by absorption: a serum preparation was incubated for 2 hours with a 20 per cent emulsion of normal monkey cord; the supernatant fluid after centrifugalization afforded protection against a virulent cord emulsion. Moreover, anticord properties have been demonstrated in the serum of horses that have shown no antiviral response to the immunizing treatment.

#### SERUM PROTECTION AND TREATMENT (EXPERIMENTAL BASIS)

It was early shown experimentally that the blood of recovered cases (human and monkey) not only neutralized virus *in vitro* but that this

power was effective also *in vivo*, and that the serum of artificially immunized monkeys possessed similar neutralizing properties. Although Leiner and von Wiesner (1910, L 28, III) and Levaditi and Landsteiner (1910, L 46) were unsuccessful in preventing infection by single or repeated intraperitoneal injections of monkey convalescent serum, Flexner and Lewis (1910, F 45, F 46) found that if monkeys were inoculated intracerebrally with a quantity of virus not in excess of a given dose, and if an intraspinal injection of immune serum was made 18 to 24 hours later and given daily for several injections, development of paralysis was, in some cases, prevented. The immune serum was introduced into the subarachnoid space with the expectation that it would thus come into direct contact with the virus, which was thought to establish itself first in the meninges. Repeated injections were made, in order to maintain this contact under the supposition that the virus had probably multiplied during the period between the inoculation and the first injection of serum.

By intraspinal administration of immune serum development of infection after intranasal inoculation was prevented. The first injection was made immediately after the inoculation; others were given at 3 day intervals for 3 injections.

As described in a previous section, other fluids of even slightly irritative nature set up an aseptic meningitis when injected into the subarachnoid space and thus promoted infection if given previous to an intravenous inoculation of virus. Immune serum alone prevented instead of promoting such infection (Flexner and Amoss, 1917, F 24). Immune serum injected intraspinally was also effective in preventing infection even when meningeal irritation had already been produced by a previous preliminary intraspinal introduction of normal horse serum (Flexner and Amoss, 1914, F 22), of normal monkey serum, or of normal salt solution (Flexner and Amoss, 1917, F 24). When isotonic salt solution was used, 1 dose of immune serum at the time of the intravenous injection of virus was sufficient to prevent symptoms; but when the more irritative sera were used, repeated doses were necessary.

The results described above were thought to have an important bearing on the serum therapy of the disease as they showed that immune serum had the power to counteract the ill effects of a break in the barrier of the meningeal-choroid plexus complex.

Since the passage of neutralizing substances from the blood to the spinal fluid was readily demonstrated following meningeal irritation it was felt that the early use of an immune serum might anticipate the development of a sufficient quantity of these substances in the patient's



own blood. This furnished, it was believed, experimental basis for the therapeutic use of immune serum but not for the use of normal serum (Flexner and Amoss, 1917, F 23, F 26).

In the above experiments, it will be noted that treatment was, in all cases, administered with or soon after the virus inoculation. Brodie (personal communication) has been able to save monkeys by the administration of 6 cc. of convalescent serum 3 days after an intracutaneous inoculation with 1 gram of virus. The average incubation period by this route is 8 days.

Recently Howitt (1932, H 36) has described the results both of early protection tests and also of the treatment of the experimental disease in the preparalytic stage. Monkey convalescent serum was injected either intramuscularly or by the combined intraspinal and intravenous routes. The onset of the preparalytic stage was determined by the temperature curve and the spinal fluid cell count (see *Section on The Experimental Disease*). Serum given intramuscularly 24 hours before or after an intracranial injection of virus protected in 2 instances each, but not in the 2 cases in which it was given simultaneously with the inoculation; but serum given by the combined method at similar intervals afforded no protection.

Fourteen monkeys, 8 of which had been inoculated intracranially and 6 intranasally, were treated intramuscularly during the preparalytic stage; of these, 11 recovered, though all but 1 showed residual paralyses. Eleven animals were treated during this stage by the combined method; 4 had been inoculated intracranially, and the rest had received intranasal instillations; 2 of these monkeys recovered with paralysis. Of 14 untreated controls, 5 recovered but with some residual paralysis. There were no recoveries among the 14 animals treated by either method during the early or advanced stage of paralysis. (The percentages given in the summary are confusing; the percentage of recoveries and deaths in each experiment was determined, and these 5 percentages were averaged to obtain the final result.)

Howitt considered the results of these experiments inconclusive as there was neither 100 per cent cure for the treated animals nor 100 per cent fatality for those untreated. It seemed, however, that the intramuscular administration was as effective, or perhaps more effective than the combined intrathecal and intravenous method. In some instances, repeated doses of serum were given but apparently with no more effect than 1 dose (see *Chapter on Treatment*).

Protective and curative tests with sheep and horse serum have already been described in the *Section on Immune Sera*.

## PASSIVE IMMUNIZATION

Although the administration of convalescent or immune serum is not invariably successful in protecting against a subsequent inoculation of virus (Leiner and von Wiesner, 1910, L 28, IV; Oluf Thomsen, 1914, T 12), the prophylactic effect, in certain instances, has been demonstrated experimentally (Flexner and Stewart, F 53, F 54; Flexner, 1929, F 19, F 18; Rhoads, 1931, R 10). Intravenous injection of convalescent serum 24 hours before intracerebral inoculation with a suitable dose of virus afforded protection. The duration of the period of immunity provided was also tested. Convalescent serum injected intraspinally protected for 4 days against subsequent intracerebral injection of virus and sometimes for 6 days against intranasal instillation. On the basis of these experiments it has been suggested that human convalescent serum be employed for passive immunization during epidemics of poliomyelitis.

Passive immunity tests with antisera from refractory animals have been described in the *Section on Immune Sera*.

Inasmuch as many of the problems concerning immunity in poliomyelitis are still unsolved, it may be well here to recapitulate the important known facts, together with some of the theoretical considerations that are yet under discussion.

Although absolute immunity may not exist in any disease, a relatively high degree of permanent immunity to the virus of poliomyelitis has been shown to follow infection with the virus. This is evidenced by resistance to re-infection in the experimental, and the rarity of second attacks in the human disease; and by the demonstration of the power of the blood serum of convalescent human beings and of monkeys to neutralize the virus *in vitro*. Substances with inhibitory power are found both in the serum and, though infrequently, in the spinal fluid of human beings during convalescence; in the nasopharyngeal secretions or washings of healthy persons; and, in one experiment, in the bile of paralyzed monkeys.

In the animal kingdom, neutralizing substances have not been demonstrated in the serum of normal immature monkeys, though they are almost always present in the serum of convalescent and of actively immunized monkeys; the titer of convalescent monkey serum may be raised by re-injection. Even the normal serum of refractory animals, as the sheep, goat and horse, occasionally exhibits inhibitory power; and this property may be increased especially in the horse, by repeated injections of virus.



The serum of human beings who have suffered from an attack of poliomyelitis usually has neutralizing power, though the degree of protection afforded is not uniform. Neutralizing substances are frequently present in the serum of normal persons. They are found not only in the serum of individuals who may at some time have been in direct contact with the virus, but in that of persons, as Eskimos and Liberian negroes, who have suffered no known exposure. Moreover the antibody content of normal human serum is often of as high or higher titer than that of convalescent serum. Serum from cases of long standing has, in some instances, at least, neutralizing power equal to, or greater, than that from recent cases.

The tests made are as yet too few to show the effect of storage on the potency of serum. The optimum time for collecting serum after the acute illness has not been determined.

A few tests for susceptibility have been reported but additional information on this subject is needed.

The results of neutralization tests have shown that poliomyelitis is immunologically distinct from rabies, Borna's disease, or epidemic encephalitis.

Efforts to induce active immunity with killed virus have failed. The results with attenuated virus have been irregular; success has been obtained in some instances regardless of the method of modification. Greater success has attended the use of active unattenuated virus, especially when introduced by the intradermal or intrasplenic routes. Immunity does not develop as a consequence of intracerebral inoculation. Intradermal administration of virus in conjunction with the subcutaneous injection of immune serum has been employed with good results. In such experiments, neutralization *in vitro* has been shown to be a more delicate test of immunity than intracerebral inoculation.

The neutralizing substances have been found to be filterable; to be inactivated on heating to 70°C. They are water-soluble, and not volatile. Serum-virus mixtures are dissociable. Time and dilution are important factors in neutralization tests; the quantity of the inoculum determines the result rather than the potency of the virus.

The nature of the antibodies in immune serum, however, requires further study. The results of complement-fixation and precipitin tests have suggested to some workers that they resemble antitoxins rather than bacterial antibodies. To another group, however, the distribution of the antiviral substances in the protein fractions of horse serum is contrasted with that of the antitoxins.

The factors which govern the resistance of an individual to a disease are of the greatest importance both from the scientific and from the practical standpoint. The nature of the protective mechanism in poliomyelitis is of especial interest; the low rate of incidence would indicate that, in addition to the immunity which may be acquired as the result of exposure to the virus, there may be other factors which are of equal importance in the prevention of infection. A normal nasal mucosa and an intact meningeal-choroidal plexus complex have been believed to form a mechanical barrier to invasion by the virus. It has been suggested that the greater immunity to poliomyelitis as well as to some other infections, observed in adults, rests primarily on the normal endocrine balance associated with maturation.

A possible relationship between the neutralizing power of the blood serum and the production of hormones during menstruation and pregnancy has been indicated by recent experimental work. The blood group to which an individual belongs has been thought to be another factor in determining his resistance to poliomyelitis—group B being relatively immune. If one may judge by the antibody content of the serum, the immunity acquired by a normal person may be greater than that which follows an attack of the disease.

Tests carried out in the course of active immunization experiments would indicate that immunity is only relative; that it is proportional to the infectivity of the virus, slow absorption of which is necessary for its development.

In summary it may be said that there is evidence of the existence of substances specific in character, capable under certain conditions of holding the virus in an ineffective combination; but that other possible inhibitory factors, which may be nonspecific in nature, must be taken into consideration; the relation between these two is a subject for further research. Moreover, there is need for the development of a reliable and inexpensive test for susceptibility and for information concerning a specific antiviral substance, corresponding to vaccine virus, which may be used for the prevention, if not for the treatment, of poliomyelitis in human beings.



## CHAPTER IV

### SYMPTOMATOLOGY

#### EVOLUTION OF THE CLINICAL PICTURE

The evolution of a disease from the time at which it was merged with others having certain symptoms in common, to the time when it stood out as a distinct clinical entity often required many years of patient study. This is particularly true of a disease like poliomyelitis in which the symptomatology is varied and in which the etiological agent can rarely be demonstrated in the living patient.

Underwood (U 2) is often credited with being the first to describe cases of poliomyelitis. He wrote at some length of paralyses, especially of the lower extremities, in children, and occasionally in adults, which he believed not mentioned by other medical writers within the compass of his reading. His description, however, of the gradual onset, the absence of pain, fever, or any manifest disease (although he does state that the condition seems to arise from debility and usually attacks children previously reduced by fever), the speech disturbances, and the occasional impairment of intellect throws grave doubt on the probability that the cases cited by him were poliomyelitis.

Joerg (J 9) described an illness with fever in a child a few weeks of age, which had been healthy at birth. This illness lasted a long time and the child became wasted and weak. Later the mother, who had been critically ill at the same time, noticed that the child did not move its feet properly, they eventually became clubbed. While there are few references to this description of Joerg's, it is accepted by Römer (R 25) as an unquestionable picture of poliomyelitis,—as it probably is.

John Shaw in 1823 (S 34) wrote more convincingly. "But certain paralytic affections of the muscles are sometimes so instantaneous, that we must consider them as depending on a change which has suddenly taken place in the brain, or spinal marrow or in the nerves which supply the affected parts. . . . I have been told that such sudden attacks are common among children in India, and that strong and healthy children are more frequently affected than those of a more weakly constitution."

In connection with this reference, it may be noted that Goodeve (G 15) later described illnesses with paralysis in children in India, some of which strongly suggest poliomyelitis.

John Badham in 1835–1836 (B 1) reported 4 cases in which paralysis followed by atrophy developed suddenly after 2 or 3 days of drowsiness and increased thirst. In 1 instance there was also strabismus. In all 4 cases, however, there was diminution of sensation in the affected limb; in 1 instance there was swelling, and in 3 inequality of the pupils—signs and symptoms certainly most unusual in poliomyelitis.

Heine in 1840 (H 18) described 27 cases of paralysis of different degrees treated by him at an orthopedic clinic at Cannstadt. All these patients were in the chronic stage and the symptoms of the acute stage were obtained from the histories.

In certain instances, as for example the first case cited, the history suggests another diagnosis than poliomyelitis. The account is as follows: L. B., the son of healthy parents with several other healthy children, was well developed at birth. He remained well until the third year, when he contracted scarlet fever from which he recovered without complication. Shortly after this illness, having slept well during the night, he suddenly complained of feeling sick, became pale, fell down unconscious, foamed at the mouth and nose, and, apparently without convulsions, developed in a few seconds paralysis of arms, legs, bladder and intestines. About the fifth day, the paralysis of bladder and intestines disappeared and later that of the arms, while the paralysis of the lower extremities persisted. This type of onset does not in the least suggest poliomyelitis. At the present time such a case would probably be diagnosed as encephalo-myelitis following scarlet fever, if the term “shortly after” may be accepted at its face value. In another case there was loss of sensation in addition to the paralysis of the legs, suggesting a transverse myelitis. In other cases there were severe convulsions, which are unusual in poliomyelitis at the present time. This may be due to the more frequent occurrence of convulsions at that time from dietary causes, or to the modification of the course of the disease as time has passed.

In spite of these possible exceptions, it seems indisputable that most of these cases were poliomyelitis and that Heine was the first to establish the disease as a clinical entity. It would indeed have been remarkable if certain cases, which in the light of our present knowledge were probably not poliomyelitis, had not been included in the classification.

Heine called attention to the development of the disease in young children previously in excellent health; to the febrile, initiative manifestations that usually preceded the paralysis; to the distribution of the paralysis in various parts of the body; to the fact that some improve-



ment in the paralysis often takes place; and to the subsequent good health and unimpaired mentality. This discussion certainly makes a very clear-cut picture of poliomyelitis as we know it at the present time.

Kennedy in 1841, published a paper (K 8), reprinted in 1850 (K 9), in which he reported 6 instances of paralysis in infants and children. The paralysis appeared suddenly and had a tendency to disappear.

West (1843, W 15) discussed the paralyzes incidental to infancy in which he recognized 3 classes of paralysis in children: (1) those instances where it is congenital; (2) cases in which convulsions or other cerebral symptoms occur; (3) cases in which there is no evidence of cerebral disease. He cited cases of all 3 classes. In the third group mention is made of instances in which a previously healthy child awoke in the morning with paralysis. The term "morning paralysis" is attributed to West.

The first report of cases in the United States in which the diagnosis was probably poliomyelitis was made by Colmer in 1843 (C 22). He stated that while on a visit to Louisiana in the fall of 1841 his attention was called to a child about a year old which was slowly recovering from an attack of hemiplegia. He was told that during the preceding 3 or 4 months 8 or 10 other cases of either hemiplegia or paraplegia had occurred within a radius of a few miles. All the children were less than 2 years of age and they had recovered or were decidedly improved. The occurrence of a number of cases at the same time in a restricted locality suggests a small epidemic, which is confirmatory evidence of the diagnosis.

Rilliet in 1851 (R 16) published an article in which reference is made to an earlier study by himself and Barthez (R 17). Rilliet and Barthez used the term "essential paralysis" to describe this disease because they believed that the paralysis was not due to a lesion of the central nervous system. Rilliet stated that "essential paralysis" never in itself leads to death.

Seeligmüller (1878 and 1879, S 26) reported the findings in 75 cases observed by himself over a period of 11 years, which included not only well-developed children as Heine says, but also weak rachitic children. Forty-four of these were boys, 31 girls. The onset followed scarlet fever in 2 cases, measles in 1, and erysipelas in 1. In 71 cases the age of onset was under 6 years. The interval from the onset of the paralysis to the time of the examination varied from 2 days to (in 1 case) 35½ years.

The frequency with which certain symptoms were observed in 67

cases in which some information regarding the onset could be obtained was as follows:

|                                                                   |    |
|-------------------------------------------------------------------|----|
| Fever.....                                                        | 43 |
| Gastro-intestinal disturbances (vomiting, diarrhea, or both)..... | 13 |
| Convulsions.....                                                  | 11 |
| Twitching.....                                                    | 7  |
| Sudden paralysis without premonitory symptoms.....                | 6  |
| Stupor.....                                                       | 3  |
| Tremor of the body.....                                           | 2  |
| Pain in the extremities later paralyzed.....                      | 2  |

|                                                             |    |
|-------------------------------------------------------------|----|
| No knowledge of exact time of development of paralysis..... | 10 |
|-------------------------------------------------------------|----|

The distribution of the paralyses in the 75 cases was:

|                             |    |
|-----------------------------|----|
| Monoplegia.....             | 55 |
| Both lower extremities..... | 14 |
| Hemiplegia.....             | 1  |
| Crossed hemiplegia.....     | 2  |
| All four extremities.....   | 2  |
| Both upper extremities..... | 1  |

This early report of the clinical history and distribution of paralyses in so large a group of cases seems to merit attention.

Strümpell in 1884 (S 65) pointed out the resemblance between certain cases of acute encephalitis and spinal paralysis, occurring in children. He stated that the analogy between the two diseases was unmistakable. Both affect previously healthy children in the first years of life. The initial stages with sudden onset, fever, vomiting, and convulsions (convulsions seem to be one of the most constant of the initial symptoms in acute encephalitis) can scarcely be distinguished from each other. Then follows paralysis which is evidenced in both by involvement of the motor nerve system. The paralyses are different in type. In the encephalitic type there is no degenerative atrophy and no reaction of degeneration although the affected extremity may be smaller in circumference and shorter, owing to inhibition of growth. There is a definite muscle tension, making severe contractures infrequent, and increase in the tendon reflexes.

For this type of case Strümpell suggested the name cerebral paralysis of children or acute polio-encephalitis in contrast to spinal paralysis of children or acute poliomyelitis. He expressed the belief that the two diseases were closely related or perhaps were identical in the sense that it is the same—*perhaps infective*—agent localized in the one case



in the gray matter of the cord and in the other in the gray cortex of the brain.

Strümpell is therefore to be credited with describing the encephalitic type of poliomyelitis; but the description which he gives of the later stages of the disease suggest that some of his cases would be diagnosed today as epidemic encephalitis. The description is as follows: "In a number of cases, signs of motor irritation persist. Many patients show symptoms of epilepsy through life. In some the epileptic convulsions are confined to the affected side, but more frequently they are generalized epileptic seizures. Athetosis, chiefly of the hands, follows more often than epilepsy. Disturbance of speech sometimes appears; more often, a diminution of intelligence and moral deterioration are observed."

Pierre Marie in 1885 (M 16) called attention to the similarity between infantile cerebral hemiplegia and infantile spinal paralysis.

He describes an instance reported by Möbius and Sängner (1884, M 39). A brother and sister became ill on the same day with fever and constitutional symptoms. One child developed a hemiplegia and the other a spinal paralysis.

The cerebral type of poliomyelitis is, therefore, often called the Strümpell-Marie type.

The work of Cordier has received far less attention than it deserves. In 1888 (C 26) he published the results of observations on 13 cases that occurred in June and July of 1885. Cordier did not see these cases in the acute stage. His attention was directed in 1886 to this small epidemic and he visited the district to collect the case histories. He stated that he hoped "in showing that atrophic paralysis of childhood can occur in epidemics to bring out also the fact that this paralysis is a specific, infectious disease, perhaps microbic."

He called attention to the acute onset in children in excellent health, to the fever and profuse sweating, to the development of the paralysis on the second or third day, and to the variable extent of the paralysis. Most important of all he reported the death of 4 children from bulbar paralysis—this being the first record of this particular form. He pointed out that the general belief that infantile paralysis rarely endangered life was incorrect and suggested that it is probably much more often fatal than is recognized, many children dying without parents or doctors suspecting the nature of their illness.

Medin shares with Heine much of the credit for the development of the conception of the various phases of poliomyelitis. He was the

TABLE 1  
SUMMARY OF SYMPTOMS OF AN EPIDEMIC OF INFANTILE PARALYSIS\*

|                                                                                                                                                                  | MAY | JUNE | JULY | AUGUST | SEPTEMBER | OCTOBER | NOVEMBER | TOTAL |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|------|------|--------|-----------|---------|----------|-------|
| Acute anterior poliomyelitis with paralysis of the extremities.....                                                                                              | 2   | 1    | 2    | 8      | 8         | 4       | 2        | 27    |
| Facial monoplegia.....                                                                                                                                           |     |      |      | 1      | 1         | 1       |          | 3     |
| Acute polyneuritis.....                                                                                                                                          |     |      |      | 2      |           |         |          | 2     |
| Acute polyneuritis with paralysis of the abducens and hypoglossal.....                                                                                           |     |      |      | 1      |           |         |          | 1     |
| Acute polyneuritis (?) ataxic and spastic symptoms and paralysis of the facial nerve.....                                                                        |     |      |      |        | 1         |         |          | 1     |
| Acute polyneuritis (?) ataxic and spastic symptoms and acute nephritis.....                                                                                      |     |      |      |        | 1         |         |          | 1     |
| Acute polyneuritis (with acute anterior poliomyelitis) and paralysis of the facial nerve.....                                                                    |     |      |      | 1      |           |         |          | 1     |
| Acute anterior poliomyelitis with paralysis of the abducens.....                                                                                                 |     |      |      |        | 2         |         |          | 2     |
| Acute anterior poliomyelitis with paralysis of the facial and oculomotor.....                                                                                    |     |      |      | 1      |           |         |          | 1     |
| Acute anterior poliomyelitis with paralysis of oculomotor and vagus.....                                                                                         |     |      |      |        | 1         |         |          | 1     |
| Acute anterior poliomyelitis with paralysis of facial, vagus and spinal accessory....                                                                            |     |      |      |        | 1         |         |          | 1     |
| Acute anterior poliomyelitis with paralysis of spinal accessory and hypoglossal.....                                                                             |     |      |      |        | 1         |         |          | 1     |
| Acute anterior poliomyelitis with paralysis of oculomotor, abducens (external ophthalmoplegia), facial, trigeminal, vagus, spinal accessory and hypoglossal..... |     |      |      |        | 1         |         |          | 1     |
| Acute poliencephalitic with paralysis of the abducens.....                                                                                                       |     |      |      | 1      |           |         |          | 1     |
| Total.....                                                                                                                                                       | 2   | 1    | 2    | 15     | 17        | 5       | 2        | 44    |

\* Medin (Verhandl. d. X. Internat. med. Kongr. 1890, 2: Abt. 6, 37, 1891).

first to study an epidemic of any considerable size. In 1887, from May to November he saw 44 cases (M 32). He reported this epidemic in August, 1890.

Among symptoms he listed: fever, somnolence, gastro-intestinal disturbance (in some cases vomiting, in some diarrhea, in most con-



stipation), irritability, pain and restlessness. Convulsions were observed only twice. In some cases there was a fever-free remission, then a return and a spread of the paralysis. In a few cases there was complete restitution of the paralysis, in some cases it was almost complete. Polyneuritis and ataxia were noted. He also reported bulbar symptoms.

The location of the paralyses is given in Table 1.

Medin concludes: "Infantile paralysis is without doubt an acute, infectious disease—an entity. It may, as some observers in the last decade have shown, appear in epidemics. Cordier believes that the disease is contagious, but I have no certain proof of this conception although I have at times seen that two children in the same family became sick within an interval of a few days.

"My observations have made it clear that the gray anterior horns of the spinal cord are not the only parts of the central nervous system affected. In the acute stage, indeed, the whole organism is affected. In some cases there seems to be at least a functional disturbance of the central nervous system that is very widespread. In most cases the gray anterior horns of the cord are most affected but in others the peripheral nerves and the cerebral cortex are affected. Most probably all nerve nuclei in the medulla and pons may be attacked. The symptom complex changes according to the portion of the central nervous system most affected, but whether the disease shows itself as poliomyelitis, as polyneuritis, or as acute polio-encephalitis—all these differently localized forms belong genetically to one and the same disease."

Caverly in the summer of 1894 observed an epidemic of more than 100 cases in Otter Creek Valley, Vermont. This epidemic was first reported in that year (C 3; C 4); later at more length (C 6). A detailed epidemiological study was made and also a careful analysis of the symptoms and the location of the paralyses. Attention was called to the occurrence of muscular rigidity—of the neck or back muscles—and also to hyperesthesia of the skin. The most outstanding contribution of the article is the recognition of 6 cases of the nonparalytic type. This is the first time this form of the disease is mentioned, and its importance can hardly be over-estimated.

Until his death in 1918 Caverly was "a leader and tireless worker in the field of the prevention and treatment of infantile paralysis." Through his efforts Vermont became the first state to institute a comprehensive plan for the after-care of sufferers from infantile paralysis.

His many contributions to the problem have been collected in a volume "Infantile Paralysis in Vermont" published in 1924 as a memorial to him.

Wickman is often credited with being the first to describe the abortive (including the nonparalytic) type of poliomyelitis. This distinction really belongs to Caverly. But Wickman's contributions to the knowledge of poliomyelitis—his careful epidemiological, clinical, and pathological studies—place him with Heine, Medin, and Caverly. Wickman's Monograph on "Acute Poliomyelitis (Heine-Medin's Disease)" (W 21) is a real classic and deserves careful reading by all interested in infantile paralysis. Indeed, Wickman's description of the symptomatology is so complete and detailed that little has been added by later writers.

### SYMPTOMATOLOGY

In discussing the symptomatology of poliomyelitis one must remember that the predominating symptoms vary in different epidemics and at different stages of the same epidemic. The symptoms are determined by the systemic response to the infecting agent and by the degree of invasion of the central nervous system. While the virus has a predilection for the motor cells of the anterior horns of the cord, it may occasionally attack other parts of the central nervous system, thus giving rise to a varied clinical picture.

**Incubation Period.** The incubation period of the disease has been considered elsewhere in some detail (see *Chapter on Epidemiology*). From such evidence as is available, it seems that the incubation period is probably rarely less than 6 or more than 18 days; usually it is from 7 to 14 days.

**Types of Onset.** The initial symptoms are much the same in all types of the disease and they may be quite as severe in the nonparalytic as in the paralytic forms.

While the onset may, rarely, be insidious, in the vast majority of cases it is very abrupt. Three types of onset may be described. The earlier writers, as Shaw and West, stated that in some instances previously healthy children awoke in the morning with paralysis. This was later corroborated by others: Seeligmüller (S 26); Gossage (G 16); Römer (R 25). There has been a tendency recently to question the existence of this type of onset and to claim that prodromal symptoms had really been present but had escaped notice. However, there are certainly cases, relatively rare, it is true, in which careful questioning of intelligent



parents fails to elicit the existence of symptoms before the development of paralysis. Jenkins (J 7) noted that in 11 out of 191 cases paralysis was the first symptom.

A second and more common type of onset is that in which there is a period of remission in the development of the disease. This type was mentioned first by Medin (M 32), and later by Kling and Levaditi (K 12), Wickman (W 21) and others. Draper (D 18) has emphasized this as the dromedary type. In these cases the disease is ushered in with somewhat indefinite symptoms of a gastro-intestinal or anginal nature, with fever. This lasts for a few days after which a remission of from one to several days occurs during which the patient seems quite well. A recurrence of the systemic symptoms then takes place, with indications of an invasion of the central nervous system which usually goes on to paralysis.

By far the most common type of onset, however, is that in which the symptoms of systemic infection progress rapidly and uninterruptedly to those indicating an involvement of the central nervous system.

**Symptoms.** The early symptoms of the systemic infection are headache, fever, vomiting, constipation or diarrhea, and not infrequently a congestion of the throat and pharynx. The symptoms relating to the gastro-intestinal and respiratory tracts are not necessarily present in every case. Their incidence varies greatly in different epidemics and even in different districts in the same epidemic. It is not necessary to discuss these symptoms in detail as they are not particularly diagnostic of poliomyelitis and differ in no way from those occurring in mild upper respiratory or gastro-intestinal disorders.

Fever is the most constant as well as one of the earliest symptoms. While the temperature may be as high as 104° or 105°F., more often it is from 100° to 103°F. It has no characteristic curve. It usually lasts from 4 or 5 to 10 days or longer and falls by lysis more often than by crisis. Occasionally a secondary elevation of temperature occurs, often but not always accompanied by an extension of the paralysis. The pulse rate is usually in proportion to the fever (Weisenburg and Leopold, W 13). A much more rapid rate may indicate, according to Müller (M 52), an early bulbar involvement, and it has been my own observation that such a rate not infrequently forecasts a poor prognosis. Hyperesthesia is often an early symptom, more diagnostic than the fever which, of course, occurs at the onset of most infections. This hyperesthesia may be quite general and elicited by the lightest touch, but it is usually more marked along the spine and over the large nerve

trunks and is demonstrated by somewhat deep pressure. In dealing with very young children it is difficult to differentiate between pain due to hyperesthesia and that due to passive motion. Hypoesthesia and anesthesia almost never occur in poliomyelitis. In rare cases there may be diminution of sensation over a small area. Leake (L 19) explains this on the basis of the overlapping of the "root fields" so that it takes a considerable cord injury to produce a loss of sensation in any area. Pain is an almost constant symptom of the early stages. Headache occurs in a large percentage of cases. There is often pain in the neck, back, abdomen, or extremities. At times the pain in an extremity presages an oncoming paralysis. The pain varies greatly in its severity. Not infrequently sedatives or even opiates are necessary to control it. The duration is usually short but in some instances the neuritic pains may persist even into convalescence.

A symptom-complex of diagnostic value is extreme drowsiness alternating with irritability when disturbed. Occasionally this drowsiness may progress to a state of semi-stupor or stupor lasting for several days. Delirium is on the other hand rare in poliomyelitis.

Tremors or twitchings of groups of muscles are occasionally early symptoms. Ataxia occurs in rare instances. Convulsions are relatively rare, at least in the more recent epidemics. In the early reports their frequency and severity were emphasized.

Meningeal symptoms occurring early are: antero-posterior stiffness of the neck, and especially of the back; often a moderate Kernig's sign, and Brudzinski's and Macewen's signs. The stiffness of the neck and back was noted by Caverly in 1894 and the importance of this symptom has been emphasized by numerous writers since that time. Although usually less marked than early in meningitis, it is probably due to the same factor, namely, an inflammation of the meninges over the posterior nerve roots, which causes pain when the spine is flexed.

Changes in the reflexes are most important. Early in the disease the deep reflexes are usually exaggerated and equal. At times a Babinski or an ankle clonus may be present. As the disease advances, the deep reflexes may become unequal, diminished, or lost, especially if a paralysis is about to develop. The superficial reflexes are present unless there is a paralysis of the underlying muscles. The pupils are usually equal and the pupillary reflexes are almost invariably normal. In the rare instances in which the reaction to light is sluggish the change may perhaps be due to a greatly increased spinal fluid pressure. This alteration occasionally occurs even in cases of meningism.



Profuse sweating was emphasized by Müller as an early symptom of diagnostic importance. Wickman corroborated this statement (W 21), but almost all recent writers have made few comments on this point. Peabody, Draper and Dochez (P 7) state that in a few instances there was general and profuse sweating and that sweating occurred in numerous cases in localized areas.

Retention of urine, necessitating catheterization, occasionally occurs. More frequently there is some difficulty in voiding. In severely paralyzed cases there may be incontinence.

Cutaneous lesions are rare, and, when they do occur, are probably purely incidental to the disease process, except in so far as an erythematous rash may appear in any acute febrile condition. Herpes labialis or herpes zoster are most unusual.

A description of the early symptoms gives a very inadequate picture of the disease. The severity and nature of the symptoms listed varies in different outbreaks, and especially in individual patients. In some patients the meningeal symptoms are particularly marked; in a smaller number, the disturbances of the sensorium; in others, the pain and hyperesthesia; in still others, the tremors, muscular twitchings, and other motor phenomena; and occasionally in others, disorders of the gastro-intestinal or upper respiratory tract.

If paralysis—which is usually subcortical in type—occurs, it most often develops on the second or third day of the disease—except in the “dromedary” type—but it may be delayed until the eighth day or, rarely, later. Premonitory signs of an approaching paralysis, such as pain, diminution or loss of the deep reflexes, tremor or twitching of groups of muscles, or weakness, may be present, or the paralysis may develop suddenly without warning. In some instances the paralysis reaches its maximum almost immediately. In others, additional paralyses develop over a period lasting from a few hours to 2 or 3 days. In the ascending type of paralysis, resembling Landry’s, or in the descending type—both of which usually progress to the involvement of the medulla—the pathological process may progress for several days, occasionally interrupted by a period of remission.

Very rarely it happens that after a period of 2 or more weeks of apparent quiescence, the paralysis progresses. This condition will be discussed in the *Section on Relapses*.

There is apparently considerable difference in the distribution and severity of the paralyses in different epidemics. From tables given by Lovett (L 71) and by Wernstedt (W 14), it appears that one or both

legs are most frequently involved (see Tables 2 and 3). From Lovett's data the following facts appear: When one leg and one arm were affected, a hemiplegic distribution was more common than a crossed distribution; paralysis of abdominal muscles was present in 72 per cent

TABLE 2  
DISTRIBUTION OF PARALYSIS IN 1529 CASES IN NEW YORK STATE\*

|                                          | 1916 CASES | CASES<br>AFFECTED<br>PRIOR TO 1916 |
|------------------------------------------|------------|------------------------------------|
| Both legs.....                           | 338        | 127                                |
| One leg.....                             | 302        | 85                                 |
| Both legs and both arms.....             | 127        | 55                                 |
| Both legs and one arm.....               | 101        | 43                                 |
| One arm.....                             | 83         | 19                                 |
| One arm and one leg, same side.....      | 38         | 13                                 |
| One arm and one leg, opposite sides..... | 29         | 7                                  |
| Both arms.....                           | 33         | 4                                  |
| Both arms and one leg.....               | 20         | 8                                  |
| Girdle cases.....                        | 57         | 1                                  |
| Facial alone.....                        | 38         | 1                                  |
| Total.....                               | 1,166      | 363                                |

\* Lovett (Treatment of Infantile Paralysis, 2nd ed., Philadelphia, P. Blakiston's Son & Co., 1917).

TABLE 3  
SUMMARY OF DISTRIBUTION OF PARALYSES THROUGHOUT THE BODY\*

| LOCALIZATION         | TOTAL NUMBER OF CASES: 5748 |                   |
|----------------------|-----------------------------|-------------------|
|                      | Number                      | Per cent of total |
| Cranial nerve.....   | 767                         | 13.3              |
| Throat and neck..... | 333                         | 5.8               |
| Trunk.....           | 1,601                       | 27.8              |
| Arm.....             | 2,372                       | 41.3              |
| Leg.....             | 4,519                       | 78.6              |

\* Wernstedt (Ergebn. d. inn. Med. u. Kinderh. 25: 705, 1924).

of one group of cases, of the muscles of the back in 13.5 per cent, and of the neck in 11 per cent. The sphincters were rarely involved.

It does not seem necessary to give a long and detailed description of the various combinations of paralyses that may occur. If one remembers that any muscle or combination of muscles may be affected to



degrees varying from weakness to complete loss of power, one will have a good general idea of the lower motor neuron type of poliomyelitis. The distribution of the paralysis is often irregular. MacAusland (M 1) writes: "The final localization of the paralysis varies exceedingly. A particularly striking feature is its unsystemic distribution; the most peculiar combinations may occur, such as a paralysis of a peroneal muscle and a deltoid, or the involvement of the muscles of one leg and the face. The loss of function is more frequently partial than total, but cases of complete paralysis are more common than is ordinarily supposed."

If a more detailed account is desired, reference may be made to Wickman (W 21), Peabody, Draper and Dochez (P 7), Ruhräh and Mayer (R 58), and Weisenburg (W 12), where full descriptions and case histories may be found.

In certain instances however, the progress and the localization of the paralysis is so important from the viewpoint of prognosis that some discussion of these forms must be given. Practically all fatalities in poliomyelitis are due to respiratory involvement, either to complete paralysis of the muscles of respiration or to a bronchopneumonia following a partial paralysis. Many physicians designate these cases as instances of the bulbar type. This classification is incorrect for most of them belong to the bulbo-spinal or to the spinal type. Weisenburg (W 12) states that of 168 deaths, in only 26 was the medulla implicated. He classes as bulbar only cases involving the medulla, whereas the majority of authors refer to cases with localization in either the medulla or pons as bulbar.

Wickman employed the term "the form resembling Landry's paralysis" for the group in which the pathological process spreads up, or more rarely, down, the spinal cord, often involving the bulb. Weisenburg says, "it is interesting that bulbar symptoms were often either the beginning or termination of the Landry type of paralysis." One can do no better than to quote Wickman's own description of these cases.

"After initial general symptoms, paralysis in the legs develops and progresses upwards to attack first the muscles of the abdomen and back, then the arm and neck, and finally bulbar symptoms appear. Cranial nerves are attacked, and as the respiratory center is implicated, dyspnea appears. Death occurs on the third or fourth day. Generally, consciousness remains clear until the very end; more rarely, coma precedes death; occasionally, Cheyne-Stokes' respiration appears. Sensibility is either normal or only slightly reduced.

"If the disease progresses so far as to produce respiratory disturbances the issue is usually fatal. If recovery does take place, signs of a widespread spinal type of the disease occasionally associated with paralysis of isolated cranial nerves persist.

"Rarer than the ascending is the descending type. According to Landry's original description, the symptoms appear in the region of the bulb and thence extend downwards. This descending type is very rare. But such forms as begin in the arm, attack then the leg and finally the bulb. Forms intermediate between ascending and descending paralysis are usually classified as 'descending.' Occasionally the legs may be spared altogether, and the arm paralysis be immediately succeeded by respiratory difficulty. The patient then quickly sinks."

An idea of the relative proportion of the ascending and descending forms may be gained from Weisenburg's figures. "Of 168 deaths, 84 were the result of the ascending type, 17 of the descending type of Landry's paralysis. In 41, death was supposedly the result of the spinal form of paralysis, but in practically all, whether Landry or spinal forms, death was the result of respiratory paralysis."

Not all cases with respiratory paralysis die. The paralysis may involve only the intercostal muscles, or the intercostal muscles on only one side; or the diaphragm alone may be paralyzed, completely or in part. In any of these events recovery may take place. Even when there is very complete involvement of all the muscles of respiration, restoration of function may follow a period in a respirator.

During the latter part of the epidemic of poliomyelitis in New York City in 1931, Dr. Emanuel Appelbaum saw a group of 5 cases which presented a uniform and unusual picture. After the usual symptoms of onset, apathy developed, together with profound asthenia of the whole body, to such a degree that there was difficulty even in eating or speaking. At this stage there was no true paralysis, except an internal strabismus in one patient. While the reflexes were present early, they were abolished as the disease progressed. The temperatures were only moderately elevated, 101° to 103°F. The pulse and respiration rates were generally rapid and there was definite cyanosis and a moderate degree of dyspnea. After the development of these symptoms—apathy, asthenia, cyanosis, and dyspnea—death ensued in from 24 to 48 hours although 4 of these 5 patients were placed in respirators. This sudden death would seem to indicate an involvement of the vital centers, because patients suffering from paralysis of the muscles of respiration usually live for a longer time in a respirator.



Medin was the first to give a detailed account of the purely bulbar type of poliomyelitis. Since that time these cases have been generally recognized and are described in all comprehensive studies of the disease. Most writers use the term to apply to lesions in both the medulla and pons. Weisenburg separates these lesions, using the word bulbar only in referring to involvement of the medulla. While in the majority of cases spinal paralyses are associated with the bulbar lesions, the purely bulbar type is by no means rare. At times there may be only one cranial nerve involved, most often the facial or abducens. Again there may be various combinations of cranial nerve paralyses. The glossopharyngeal is not infrequently affected, with resulting difficulty in swallowing and a nasal voice. Involvement of the vagus results in difficulty in swallowing, in hoarseness or aphonia, and in disturbances of the pulse rate—irregularity or tachycardia—and of respiration. Cheyne-Stokes breathing may sometimes occur. The spinal accessory and hypoglossal nerves are also occasionally involved. Wickman and also Peabody, Draper and Dochez call attention to the transient ataxic symptoms and increased deep reflexes of the leg that may develop owing to the implication of the nerve tracts passing through the brain stem. The mortality of the purely bulbar type of the disease is not high according to Peabody, Draper and Dochez, Weisenburg, Ruhräh and Mayer, and others. To quote Peabody, Draper and Dochez, "One might expect to see death from involvement of some of the higher centers, but this has not occurred in our experience, nor have we noted any tendency for a bulbar paralysis, once definitely established, to spread to the phrenic or upper cervical centers."

Cases in which death is apparently due to lesions of these higher centers are, however, occasionally seen. In our "Study of Poliomyelitis" (N 3) reference is made to a few instances in which death occurred without respiratory paralysis. In 1 case there had been intervals of great irregularity of the heart, although physical examination showed the heart to be apparently normal for 24 hours preceding death. The following description of another fatal case is quoted:

"I. F., aged 2 years. The illness began July 26, 1916, with facial paralysis. The spinal fluid showed pathologic changes, such as are commonly found in poliomyelitis. Death occurred July 31, no signs of paralysis of the respiratory muscles having developed. The microscopic pathology of this case showed the lesions of poliomyelitis present only in the pons and bulb."

In other instances in which recovery took place there was evidence of a

transient involvement of the cardiac or respiratory centers, as shown by marked irregularity of the pulse rate or of respiration.

More careful studies regarding the possible involvement of the higher centers are needed.

Ruhräh and Mayer (R 58) noted cranial nerve involvement in 46 out of 338 cases seen at the Queensboro Hospital, in the New York epidemic of 1916. In 2 cases there was conjugate paralysis of the eyes. The distribution of the cranial nerve involvement is given in the following summary:

|                       |          |
|-----------------------|----------|
| Optic.....            | 2        |
| Oculomotor.....       | 2        |
| Fourth.....           | 1        |
| Abducens.....         | 12       |
| Facial.....           | 26       |
| Glossopharyngeal..... | 2        |
| Hypoglossal.....      | 1        |
|                       | <hr/> 46 |

The muscles affected by cranial nerve palsies are listed by Wernstedt (W 14) for his 767 cases as follows:

|                             |     |
|-----------------------------|-----|
| Eye muscles.....            | 231 |
| Facial muscles.....         | 314 |
| Muscles of deglutition..... | 245 |
| Tongue muscles.....         | 43  |
| Speech muscles.....         | 121 |
| Muscles of mastication..... | 22  |

It may be noted that the facial and abducens are the cranial nerves most frequently involved.

There are occasional references to involvement of the optic nerve. In a few instances transitory blindness has been reported, and also, though rarely, optic neuritis. The olfactory nerve is never involved, so far as I can learn, nor is there disturbance of hearing. In 1 case, described to me by Dr. Jean Macnamara, there was apparent involvement of the labyrinth. The patient suffered for several months from dizziness and nausea.

In a fairly large percentage of cases, a percentage that is by no means agreed upon, paralysis does not occur. The nonparalytic type has been recognized in recent years with increasing frequency. It is highly significant from an epidemiological standpoint. Moreover, the general realization that it may run a benign course, leaving no residuals but conferring immunity, robs the disease of some of its terror. The early



symptoms may be quite as severe and varied in the nonparalytic cases as in those that go on to paralysis.

The diagnosis is made on the clinical symptoms and the spinal fluid findings that are accepted as being characteristic of poliomyelitis. Since it occasionally happens that the spinal fluid picture is essentially normal, even in the paralytic form of poliomyelitis, it is probable that a normal spinal fluid may also be found at times in the nonparalytic form. Such a finding doubtless causes failure to diagnose certain cases of nonparalytic poliomyelitis.

Abortive poliomyelitis has been extensively discussed in recent years. By this term is now meant the form of the disease that is limited to a systemic infection with fever, headache, malaise, and perhaps gastrointestinal symptoms, with no indication of involvement of the central nervous system. Wickman used the term to include not only this type but also the type with signs of meningeal irritation, which is now called the nonparalytic form.

It is obvious that a diagnosis of the abortive form of poliomyelitis can rarely be made with any degree of certainty. Poliomyelitis occurs most often during the hot weather when young children are prone to develop gastro-enteritis, and upper respiratory infections may of course take place at any season. In the absence of clinical signs of involvement of the central nervous system and of changes in the spinal fluid a diagnosis of poliomyelitis cannot be made by ordinary methods. If serum neutralization tests were done both before and after the illness, a positive diagnosis could be made. Or if the serum after the illness showed a high neutralizing power, the evidence would be most convincing. An important contribution to this problem was made in the summer of 1931 by John R. Paul, who wrote in a personal communication to Dr. W. H. Park: "...we found the poliomyelitis virus in two out of twelve cases of minor illness that had mild symptoms characterized by headache, fever, vomiting and sore throat... These cases did not subsequently show any signs by which the diagnosis of polio might be made. Unless they had come from a family or group, in which another case of recognizable poliomyelitis had existed, we would have disregarded the illness as trivial. There is some evidence... [for] the contention that these minor illnesses represent the first 'hump' in the so-called 'dromedary type' of the disease. This evidence rests largely on the fact that the symptomatology of the first 'hump' corresponds more closely to that of the minor illnesses than does that of the second 'hump.' Furthermore, in a few families (but not more than 10-15

per cent of those studied) the first 'hump' of the known case corresponded in time to an outbreak of minor illnesses among other members of the family. The interpretation of such a situation would, of course, rest upon the hypothetical fact that all members were infected simultaneously."

The virus was demonstrated by the inoculation of oral washings into monkeys on the first and second days of illness.

Paul's work is good evidence that an infection with the virus of poliomyelitis may take place without involving the central nervous system. To what extent this type of infection occurs will remain a matter of conjecture, in view of the present difficulties of proof, until some simpler method of diagnosing an abortive attack of poliomyelitis is devised.

Three types of poliomyelitis have thus far been described: the abortive type, in which the central nervous system is not involved and in which a definite diagnosis is usually impossible; the nonparalytic type, in which the central nervous system is attacked but not to such an extent as to produce paralysis; and the type with subcortical paralysis. The last two types constitute the great majority of cases that are definitely diagnosed as poliomyelitis.

While the virus apparently has a distinct predilection for the motor cells of the anterior horns of the cord, it may occasionally attack any one or several parts of the central nervous system, giving rise in small groups of cases to widely varying clinical pictures. Two additional types that are usually described are the encephalitic and the ataxic.

In discussing the encephalitic type of poliomyelitis it is necessary to refer to the description originally given by Strümpell (S 65) and to the statements made that at the present time cases showing the symptoms that he describes in the later stage of the disease would be diagnosed as epidemic encephalitis. Before epidemic encephalitis was recognized as a clinical entity, therefore, the diagnosis of the encephalitic type of poliomyelitis was made with much more assurance than it is today. During an epidemic of poliomyelitis, cases are occasionally seen which are diagnosed as the encephalitic type of poliomyelitis, more on the fact that they are occurring in the midst of an epidemic than on any clinical features that would distinguish them from epidemic encephalitis. In times when there is no epidemic, the diagnosis of such cases is even more difficult. Indeed the suggestion has been made by good authorities, in discussion if not in published papers, that a revision of our classification of poliomyelitis may be necessary, with a transfer of the encephalitic type to the category of epidemic encephalitis. Holt



and Howland in the latest (eighth) edition, "Diseases of Infancy and Childhood" (H 30) omit the description of a cerebral form.

We have taken some pains therefore to discover what scientific basis there is for an encephalitic type. So far as we can learn the virus of poliomyelitis has never been isolated from a case in which this clinical diagnosis has been made.

The evidence afforded by pathology is doubtful. There are few reports of microscopic examinations of the central nervous system in cases diagnosed as the encephalitic type of poliomyelitis. Webster (W 7) reported a case of poliomyelitis with deep stupor suggesting cerebral involvement. On autopsy there was edema of the pia-arachnoid over the convexity of the brain but the lesions were almost entirely in the bulbo-spinal region. Wickman (W 21) described 2 cases of Harbitz and Scheel, in which lesions were demonstrated in the cerebrum. The clinical descriptions, however, apply quite as well to epidemic encephalitis as to the encephalitic type of poliomyelitis. Even in the pathology there is no sharp dividing line between the types of certain lesions in the two diseases.

It is true, however, that involvement of the cerebrum is sometimes demonstrated in cases of the subcortical type. Therefore it is evident that the virus of poliomyelitis may invade the brain.

Experimental poliomyelitis in monkeys furnishes more proof of the occurrence of an encephalitic type of the disease.

Flexner and Lewis (F 47) state that in 8 out of 81 monkeys the paralysis at onset was of the cerebral or bulbar type. The relative incidence of these two types is not indicated. They give the following description:

"The onset of symptoms in the bulbar or cerebral group has not been the same in any two cases, and death has occurred before the development of flaccid paralysis. The striking features of the cases have been spasticity of the limbs, marked incoördination resulting in violent pseudo-convulsions; epileptiform convulsions with tonic and clonic muscle-spasms; and, finally, sudden death of an apoplectiform type. Death has occurred within thirty minutes of the first appearance of cerebral symptoms."

Römer (R 25) discussed bulbar and cerebral forms of experimental poliomyelitis in monkeys, evidently classifying instances of cranial nerve paralysis as the cerebral type, a classification which is not correct. He does, however, give a brief description of a pure cerebral type as follows:

"Monkey No. 27 (Mangabey) received on March 3, 1910, an intracerebral injection of 6 c.c. of an emulsion of virus No. 12.

"March 3-10—Remained well.

"March 11—Depressed.

"March 12—Clearly ill, breathing heavily.

"March 13—Frequent tremor of the whole body. Walks stiffly and with difficulty, but is not definitely paralysed.

"March 14—Lies on the floor; extremities show violent tremors and are stiff. Died at 4 p.m.

"On microscopical examination typical poliomyelitis. The changes affect the pia mater in the region of the central gyri; much perivascular infiltration in the cerebral cortex and basal ganglia. Very slight, apparently only beginning, changes in the spinal cord." And he adds: "Relatively seldom therefore a purely cerebral type of experimental poliomyelitis occurs in monkeys."

We are indebted to Dr. Maurice Brodie, of McGill University, for data on the development of an encephalitic type of lesion following a subcortical lesion in experimental poliomyelitis; of which the following is an abstract:

In a monkey inoculated intracerebrally with a serum-virus mixture, the usual spinal type of paralysis developed after an interval of 15 to 16 days. Twenty-four hours after the height of paralysis, or 60 hours after the onset, the animal showed symptoms of encephalitis: typical epileptiform convulsions occurred, with cyanosis, biting of the tongue, conjugate deviation of the eyes (to either side), twitching of the facial muscles (drawing the face to either side), and blepharospasm. Spinal fluid obtained by cisternal puncture showed 720 cells with 50 per cent polymorphonuclears, and a positive Pandy (Noguchi).

*Histological Examination.* Whereas the spinal cord, medulla, and pons showed a subsiding process with an increase of mononuclear cells in the exudate and loss of neurones through phagocytic cells, the cortex of the brain showed an acute inflammatory reaction with a meningeal infiltration mainly of polymorphonuclear leucocytes. Perivascular exudate and also focal areas of exudate occurred in the cortex but very little nerve destruction. Examination of the cerebral cortex of other animals either failed to disclose any histological changes, or showed at most an overlying meningitis and a few perivascular collars of mononuclear cells, evidence, therefore, of a chronic lesion which might easily be the result of a nonspecific reaction following the intracerebral trauma. In the case under discussion, however, a recent, acute, widespread encephalitis was present, 18 days after inoculation, irrespective of the traumatized site of inoculation, which was filled with glia cells and walled off by fibroblasts.



In the cerebellum there was an unusual degree of pathological change. Perivascular and interstitial infiltration of both polymorphonuclear leucocytes and mononuclear cells was observed in the cerebellar nuclei (the dentate, globosus, etc.), and a small amount of neuronophagia may have taken place.

As the encephalitis probably occurred 16 to 17 days after inoculation, and as a careful search of sections stained by the Gram and Jensen-Cladius methods failed to reveal organisms, it does not seem likely that it was due to secondary infection. Moreover, the virus of the motor cortex proved to have a greater degree of infectivity than that obtained 2 days after the height of paralysis; this would seem to indicate that the encephalitis, in this instance, was due specifically to the virus of poliomyelitis.

The evidence of the experimental disease, therefore, indicates that an encephalitic form of poliomyelitis can occur. The difficulties involved in making the diagnosis are well covered in an excellent article by Rothman (R 56) who reviews the literature and emphasizes the fact that cases of spastic paralysis are rarely seen in epidemics of poliomyelitis. He also points out that in certain instances an incorrect diagnosis is easily made, and cites the case described by Peabody, Draper and Dochez (P 7). This occurred during an epidemic of poliomyelitis and presented a typical picture of the cerebral type. However, the spinal fluid was normal and the serum later failed to neutralize the virus of poliomyelitis. Reference is made to the work of Ford and Schaffer (F 56), who reviewed the literature on infantile acquired hemiplegias and analyzed 19 cases occurring in apparently healthy children. The normal spinal fluid and the anatomic evidence did not support the diagnosis of an encephalitis; vascular lesions were found in a few instances; they suggest the possibility of invasion of the blood stream from latent foci of infection and of congenital defects in the cerebral arteries. From the study of the above cases Ford and Schaffer state that definite conclusions cannot be reached regarding the cause of such hemiplegias.

Rothman calls attention also to the fact that a spastic paralysis may be due to an extension of the inflammatory process into the white matter of the cord. In concluding, he states: "It seems evident that cases of hemiplegia occurring in previously healthy children do not represent a cerebral form of anterior poliomyelitis. It should be pointed out that these cases differ clinically from poliomyelitis in that symptoms characteristic of the prodromal period are practically never present or at least are a great rarity. . . . One may conclude that the clinical picture

described by Strümpell and Marie is not a disease entity but simply a syndrome due either to a non-purulent localized encephalitis (not epidemic and not poliomyelitis) or to vascular lesions." Personally I do not entirely agree with Rothman's concluding statement. It seems quite probable to me that certain of these cases may be epidemic encephalitis, as has been suggested earlier, and that some may be cerebral types of poliomyelitis, while doubtless many are due to vascular lesions. It must be emphasized that a normal spinal fluid does not rule out the diagnosis of poliomyelitis.

The clinical symptoms that a patient must present to be classed as a case of the encephalitic type of poliomyelitis are not definitely accepted by all authors. It has been pointed out that a spastic paralysis is exceedingly rare.

There are cases on record in which both an upper and a lower motor neuron paralysis has occurred. Dr. Jean Macnamara has told me of a patient in whom there was an upper motor neuron paralysis of the right leg and a lower motor neuron paralysis of the right arm. Other evidences of involvement of the upper motor neurons, such as increased deep reflexes, ankle clonus or a Babinski are seen somewhat oftener. Severe and prolonged convulsions seem to justify the conclusion that the cerebrum is chiefly involved. It is my opinion that a period of prolonged somnolence or stupor or delirium would lend weight to the diagnosis, though with this opinion many authorities disagree.

Inasmuch as many of these symptoms are common in epidemic encephalitis, an absolute diagnosis of the encephalitic type of poliomyelitis is usually quite impossible on clinical evidence. Corroborative evidence would be furnished by neutralization tests. The demonstration of the virus in the nasopharynx would be very definite proof. In fatal cases, the histological lesions cannot be differentiated with certainty from those of epidemic encephalitis. The isolation of the virus from the central nervous system of a case showing only cerebral lesions would definitely establish the diagnosis, and this has not yet been done.

The encephalitic type of poliomyelitis is sadly in need of further intensive investigation.

The ataxic type of poliomyelitis has been described since the time of Medin (M 32). But the differential diagnosis of these cases from other diseases and especially from epidemic encephalitis presents much the same difficulties as do cases of the encephalitic type. In Medin's description reference is made to alternating insomnia and somnolence, disturbances of speech, refusal or inability to speak, nystagmus, a fixed



stare without expression, combined with ataxia—all symptoms which are found in epidemic encephalitis.

Wickman (W 21) describes the ataxic type and states that in his opinion the pathologic basis is inconstant,—the lesions may be in the mid-brain, the cerebellum, or in Clarke's column. Peabody, Draper and Dochez (P 7) do not make a separate type for cases of this kind but they describe a temporary ataxia with increased patellar and Achilles reflexes in patients recovering from a purely bulbar paralysis.

Weisenburg (W 12) states: "From my observation there is no such thing as an ataxic type of poliomyelitis. There were a number of patients in whom there were distinct cerebellar symptoms, but in all with the exception of one they were in association with pontile lesions. Therefore, if such classification is to be made, the cerebellar type would be much more appropriate than the ataxic."

However, there is sufficient evidence of the involvement of Clarke's column to justify the inclusion of the ataxic type.

In the epidemics of 1916 and 1931 in New York City a few cases were seen which corresponded to this type. There were changes in the spinal fluid in most instances. The symptoms were as a rule fairly mild. There was ataxia of the arms or legs and occasionally nystagmus. Practically all cases recovered completely so far as the ataxic symptoms were concerned. Combinations of the ataxic and lower motor neuron types were also seen.

Dr. Jean Macnamara, in a personal communication, has stated that the recent cases in Australia have presented symptoms somewhat different from those previously observed in Australia, and from those usually observed in this country. This is of particular interest in view of the evidence presented in the *Chapter on Immunity* that a strain of virus isolated recently in Australia differs immunologically from the strains isolated here.

She stresses photophobia, which is rarely commented on elsewhere; intense hyperesthesia, persisting even for 3 months after paralysis; and a widespread coarse desquamation continuing for several months and not preceded by a rash. Since 1928, there has frequently occurred a sudden extension of paralysis after an interval of apparent quiescence and also a gradual extension of paralysis during a period of 10 days from onset.

A number of unusual involvements of cranial nerve nuclei in cases with flaccid paralyzes of the muscles of the limbs were observed. Among these may be mentioned involvement of the motor nucleus of the

fifth, with resulting paralysis of the pterygoid muscle; involvement of the vestibular nucleus of the eighth described in more detail elsewhere; bilateral involvement of the nucleus of the third nerve resulting in complete ophthalmoplegia—loss of reaction of the pupils to light and accommodation; several cases with involvement of the twelfth, eleventh, and tenth nuclei evidenced by paralysis of muscles of the tongue, of the sterno-cleido-mastoid and trapezius muscles and the muscles of the pharynx and palate. These cranial nerve involvements have been observed more frequently in 1931 than in earlier epidemics.

In Australia, Macnamara states that the question of the differential diagnosis of poliomyelitis and erythredema not infrequently arises, the photophobia, irritability, atonia and desquamation of erythredema suggesting superficially the picture of the earlier stages of poliomyelitis as it has lately appeared. In a recent article (1931) Macnamara (M 11) points out that the lack of signs of meningeal irritation, the rashes, the red, swollen, and later desquamating palms and soles, and the ulceration of the mouth and gums readily establish the diagnosis of erythredema.

This problem in differential diagnosis has not occurred in my own experience and from the literature I conclude that it is uncommon except in Australia.

**Classification.** It is evident that the balance between the attack of the virus of poliomyelitis and the resistance of the individual may result in a widely varying clinical picture. There may be symptoms only of systemic invasion. The central nervous system may be involved without the development of paralysis. Or any muscle or group of muscles or combination of muscles may be partially or completely paralyzed. This has led to many classifications of the disease. No attempt has been made to report all of these classifications.

Wickman in 1907 (W 21) formulated the following classification:

1. The spinal poliomyelitic type
2. The form resembling Landry's paralysis
3. The bulbar or pontine type
4. The encephalitic type
5. The ataxic type
6. The polyneuritic type (resembling neuritis)
7. The meningitic type
8. The abortive type

This classification is founded both on an anatomical and on a clinical basis and the types overlap. For example, the form resembling



Landry's paralysis falls logically under the first type. So do the cases of the meningitic type, with lower motor neuron paralysis. It seems therefore that a simpler classification would be desirable. Such a classification was made by Müller in 1910 on an anatomical basis: (1) The spinal form; (2) the bulbar form; (3) the cerebral type; (4) the abortive type.

An even simpler classification was suggested by Peabody, Draper, and Dochez in 1912:

1. The abortive cases—cases of infection which never become paralyzed.

2. The cerebral group, containing the rare cases in which involvement of the upper motor neuron with resulting spastic paralysis is the chief characteristic.

3. The bulbo-spinal group, comprising all cases with lesions of the lower motor neuron and flaccid paralyses.

Weisenburg (W 12) made the following classification:

1. The spinal form
2. The form resembling Landry's paralysis
3. The pontine bulbar:
  - (a) Bulbar
  - (b) Pontine
  - (c) Pontine bulbar
  - (d) Pontine spinal
  - (e) Bulbar spinal
  - (f) Pontine bulbar spinal
4. Encephalitic
5. Cerebellar
6. Meningitic
7. Abortive

This classification is rather complex for general use.

As a result of our experience in the epidemic of 1916, the meningitis division of the New York City Department of Health (N 3) suggested a classification of 4 types based on location and severity of the pathological process. After further study and in consideration of Paul's work, it seems better to modify this classification into 5 types as follows:

1. Abortive type. Cases with mild constitutional symptoms in which there is no evidence of involvement of the central nervous system. The diagnosis rests on neutralization tests or the demonstration of the virus.

2. Nonparalytic type. This includes cases in which the nerve cells are not sufficiently injured to produce paralysis, although there may be a

transient weakness. If a weakness lasts for no more than a few hours or days it seems fair to assume that it is due to edema and not to injury of the cells by the virus. Some of these cases show quite marked signs of meningeal irritation.

3. Type with subcortical paralysis. This group includes the cases with the usual spinal paralysis, also the ascending and descending types of paralysis, and the bulbar forms, with paralysis of the cranial nerves.

4. Cerebral or encephalitic type, either with or without an upper motor neuron paralysis. A spastic paralysis is rare. More often are seen evidences of involvement of the upper motor neuron such as increased reflexes or severe and prolonged convulsions. Under this type also belong those cases with marked disturbances of the sensorium, especially extreme and prolonged drowsiness or stupor. This type is relatively rare.

5. Ataxic type. The motor nerve cells are evidently not involved but there is lack of coördination, ataxia, nystagmus, etc. In some cases an ataxic gait is the only sign of involvement of the central nervous system other than the meningeal symptoms. The anatomic basis for this is proved by the post-mortem findings of involvement of the cerebellum, Clarke's column, and the intervertebral ganglia. This type is very rare.

In certain instances there are evidently multiple lesions so that various combinations of types occur—as, for instance, the ataxic and subcortical type, the ataxic and cerebral type, the cerebral and subcortical type.

**Relapses and Second Attacks.** The paralysis in poliomyelitis usually reaches its maximum within a few days after its onset, and thereafter improvement sets in. Occasionally, however, after a period of apparent quiescence, there is an exacerbation with extension of the paralysis. Reference has been made to such cases under the discussion of the course of paralyzes. At just what stage this development should be considered a relapse instead of an extension, it is difficult to decide. The persistence of the virus in the human and experimental disease is given in the *Chapter on Etiology*, and the evidence of the persistence of the acute lesions long after the clinical symptoms have subsided, in the *Chapter on Pathology*.

In one instance the virus has been recovered from the spinal cord in the human disease as long as  $3\frac{1}{2}$  months after the acute attack.

Eshner (E 18) reviewed the literature relative to relapses and second attacks. These references to apparent relapses are quoted from his paper:



"S. Auerbach (A 32) has reported the case of a child in whom two months following a febrile attack attended with paralysis of the left arm and leg a second febrile attack developed, with paralysis of the right leg.

"Rudolph Neurath (N 11) reports the case of a boy, five years old, who at the beginning of August had an attack attended with fever, pains in the arms and legs, and difficulty in walking, lasting for five days; at the end of August a repetition of the symptoms, again lasting five days; and on October 3 a renewal of the symptoms, with the addition of weakness in the upper extremities, and death on October 5. Post-mortem examination disclosed extensive degeneration of the ganglion-cells of the anterior horns throughout the spinal cord.

"E. Lövegren (L 61) has reported the case of a boy, 16 years old, in whom, two weeks following a febrile attack attended with paralysis of the left leg, paralysis of the extensors of the right thigh developed . . .

"According to M. Allen Starr (S 54), Geirsvold of Norway has reported a case in which nine weeks following an attack of poliomyelitis involving one leg, with apparent partial recovery, a second attack occurred involving the opposite leg. Starr also cites two cases of acute anterior poliomyelitis reported by Wickman in which recurrence took place at an interval of eight weeks in one and of three months in the other. . .

"Dr. Wharton Sinkler (S 45) has observed a case in which apparently two separate attacks of acute anterior poliomyelitis occurred in the same patient. In the first the right leg was involved and fairly good recovery took place, while three weeks later the left leg became involved in flaccid paralysis."

We are indebted to Dr. Lawrence W. Smith for an account of several instances in the New York epidemic of 1931 in which after periods of quiescence of from 2 weeks to 2 months, an extension of the paralysis occurred. In one of these cases there was an acute attack with almost complete paralysis of both legs. Two months later, following an ill-defined febrile illness, the boy suddenly died. At necropsy acute lesions were found in the medulla. This was evidently an instance of death due to involvement of the higher centers to which reference has already been made.

Second attacks of poliomyelitis are rare, but from the reports of reliable clinicians it is evident that they do occasionally occur. The experimental evidence is given in detail in the *Chapter on Immunity*. This indicates that complete and permanent immunity is not always conferred by the experimentally induced disease.

E. W. Taylor in 1916 (T 2) discussed the literature up to that time and reported a case that he had himself observed.

Still (S 59) has made a critical review of the reports of second attacks, 8 cases of which he has selected as acceptable, and to which he has added one of his own. Table 4 is taken from Still.

TABLE 4  
REPORTED CASES OF SECOND ATTACKS OF ACUTE POLIOMYELITIS\*

| CASE NUMBER | AUTHOR                | REFERENCE | SEX | AGES OF ATTACKS                              | INTERVAL OF ATTACKS  | PARTS AFFECTED                                                |
|-------------|-----------------------|-----------|-----|----------------------------------------------|----------------------|---------------------------------------------------------------|
| 1           | Caudouin              | C 2       | M   | 17 months<br>16 years                        | 14 years             | 1. Left leg<br>2. Right leg                                   |
| 2           | Ballet and Dutil      | B 3       | F   | 3 years<br>12 years<br>14 years              | 9 years<br>2 years   | 1. Left leg<br>2. Both arms<br>3. Both legs                   |
| 3           | Eckert                | E 5       |     |                                              | 5 years              | 1. Left leg<br>2. Right leg                                   |
| 4           | Lucas and Osgood      | L 73      | M   | 2 years<br><br>5 years                       | 2 years              | 1. Both feet and right leg<br>2. Right arm and both legs weak |
| 5           | Sanz                  | S 5       | F   | 1 year<br>15 years                           | 14 years             | 1. Left leg<br>2. Right leg                                   |
| 6           | Taylor                | T 2       | M   | 3 years<br>6 years                           | 3 years              | 1. Right leg<br>2. Left leg                                   |
| 7           | Francis and Moncrieff | F 60      | F   | 3 years<br>18 years                          | 15 years             | 1. Right arm<br>2. Both legs                                  |
| 8           | Peremans              | P 8       | F   | $2\frac{3}{4}$ years<br>$4\frac{3}{4}$ years | 2 years              | 1. Left leg<br>2. One arm                                     |
| 9           | Still                 | S 59      | F   | $1\frac{3}{4}$ years<br>$7\frac{1}{2}$ years | $5\frac{3}{4}$ years | 1. Left leg<br>2. Right shoulder                              |

\* Still (Arch. Dis. Child. 5: 296, 1930).

To the 9 cases of second attacks reported by Still I am able to add two, under my observation which seem reliable.

1. M. B., a girl 8 years of age, was seen July 15, 1922. There was a history of an attack of poliomyelitis in 1916, with a resulting paralysis



of the right leg. Her present illness was typical of poliomyelitis, the spinal fluid showed the characteristic changes, and a paralysis of the left leg developed.

2. M. K., 21 years of age, was seen September 14, 1923. He gave a history of an attack of poliomyelitis at the age of 16 months. There was a residual atrophy of both leg muscles, more marked in the left. The illness from which he was suffering presented the signs and symptoms of poliomyelitis and there was a paralysis of the muscles of the left thigh, the flexor group being particularly involved. No lumbar puncture was done as he had been ill for almost 3 weeks and was convalescing satisfactorily.

To quote further from Still: "In seeking to arrive at a solution of this question of duration of immunity, it is necessary to distinguish sharply between recrudescence and re-infection. A considerable number of cases have been recorded in which recurrence of symptoms and extension of paralysis have occurred several days or weeks after the first onset. The interval has varied from one week up to twelve weeks. Probably no one, in view of the known duration of the infection in the monkey and in the child, would suggest that these were anything but exacerbations or extensions of the original infection. . . . Apart from the many cases recorded in which symptoms of acute poliomyelitis recurred or recrudesced within three months after the first onset, there is, with one very doubtful exception (Sheppard, M 22), no case on record so far as I have been able to ascertain of recurrence of symptoms after an interval of three months until an interval of two years is reached: in other words there is apparently a silent period of two years between the time when recrudescence ceases to occur and the time when liability to a fresh attack begins to appear."

### LABORATORY AIDS TO DIAGNOSIS

The examination of the cerebrospinal fluid is of definite value in the diagnosis of poliomyelitis. The first lumbar puncture to be performed in this disease was evidently done by Schultze in 1898 (S 21). This fluid was examined for organisms and it was reported that a diplococcus resembling the gonococcus was found in the smear. Although Schultze placed some importance on this finding at the time, he later decided that it had no significance.

In 1900, Concetti (C 23) reported lumbar puncture in 10 cases of acute anterior poliomyelitis. In 4 instances organisms were found in the spinal fluids, but in 6 the cultures were sterile. It was stated that

the spinal fluid was clear; the pressure increased, 50 to 60 cc. being withdrawn; density 1.002 to 1.008; albumin content 0.4 to 0.5 per 1000.

In 1902, Triboulet and Lippmann (T 18) reported that a mononucleosis was present in the spinal fluid. This is the first reference to an increase in the cells of the spinal fluid in poliomyelitis.

This finding was corroborated by Achard and Grenet (A 7) in 1903, and by several others at about the same period, although there were records in which the spinal fluid was reported to be normal. The increased pressure was frequently noted but a complete examination was seldom made.

Wollstein (W 28), in 1908, studied the spinal fluids of 20 cases of acute poliomyelitis, centering her attention chiefly on the presence or absence of microorganisms and the reaction of complement deviation. This work is recorded in the *Chapter on Resistance and Immunity*.

In 1909, Müller (M 51; M 52) stated that in every instance in which a lumbar puncture was done (apparently in 11 out of 50 cases of poliomyelitis), the pressure was increased, the fluid was clear, the albumin was increased, chlorides were present, and cells of the mononuclear type were present in slightly increased numbers. These findings agreed with those of Krause in the same epidemic.

Netter (N 4), in 1910, referred to the occurrence of cases of poliomyelitis with meningeal symptoms and with spinal fluids showing an increase in protein and in cellular elements, largely lymphocytes.

Gay and Lucas (1910, G 5) examined 13 spinal fluids from 4 cases from the second to the seventeenth day of the disease. It was noted that in 2 instances there was a fibrin formation in the fluids. The cell counts ranged from 50 to 580 cells. In the early stages lymphocytes and small mononuclears predominated. Later large mononuclears appeared. The increase in cells was found on the thirteenth day in 1 instance and on the seventeenth day in another case.

Frissell (F 70) reported a case in which the diagnosis of poliomyelitis was made in the preparalytic stage by the examination of the spinal fluid. A second lumbar puncture was done after paralysis had developed. In both fluids there was an increase in cells, largely lymphocytes, and in protein. In the second specimen the protein had decreased. These fluids were examined by Flexner, who stated that the findings resembled those in the spinal fluid of monkeys with the experimental disease, and that this was the first instance in which he had followed the corresponding reaction in man.

Peabody, Draper and Dochez (P 7) recorded the first large series of



complete spinal fluid examinations in poliomyelitis. They examined 233 specimens of spinal fluid from 69 cases of poliomyelitis, at periods varying from the second to the sixty-fifth day of the disease. The methods used for the examination of the fluids included estimations of the pressure (which were unsatisfactory as the children were crying), estimations of the chlorides, observations on the power of reducing Fehling's solution, and on the globulin content by the butyric acid method of Noguchi. The fluids were nearly all clear and colorless. In a few instances there was a slight opalescence and, rarely, a delicate web-like clot formed on standing.

The chlorides showed no marked deviation from the normal. All fluids showed a power of reducing Fehling's solution that was practically normal. The globulin was usually increased from a slight to a well marked degree.

The cell counts in the first week of the disease varied from 7 to 1221. It is interesting to note that in several instances when cell counts were done daily or every second day, a higher count was obtained in the later than in the first examinations. The counts were as a rule less than 100 cells, but in 14 patients out of 43 there was a cell count of more than 100 in the first week of illness. The type of cell was usually the mononuclear.

There was no relation between the increase in cells and the increase in globulin. The authors state: "The commonest type of fluid seen in the whole series is one with a normal or slightly increased cell count and a well marked globulin reaction. There are, however, two other distinct types of fluid seen. One is a fluid with a high cell count and a normal or very slight globulin reaction; and the other is a fluid with a normal or low cell count and a very marked globulin reaction." The conclusions are as follows: "The spinal fluid from cases of acute poliomyelitis during the first few weeks after the onset of symptoms shows, in the great majority of instances, deviations from the normal. Fluids taken during the early days of the disease and especially before the onset of paralysis tend to show an increased cell count with a low or normal globulin content. At this early stage the polymorphonuclear cells may amount to 90 per cent of the total. Most fluids, however, show almost exclusively lymphocytes and large mononuclear cells. [Note: It is evidently from a careless reading of this statement that it is often asserted that early in poliomyelitis polymorphonuclears predominate and that they are later replaced by mononuclears.] After the first two weeks the cell count usually drops to normal, or nearly normal, and there is frequently an increase in the globulin content. A slight increase in globulin may persist for seven weeks or longer.

"Analogous changes may be found in the spinal fluid of abortive cases.

"All fluids examined reduced Fehling's solution.

"The examination of the cerebrospinal fluid in acute poliomyelitis, while giving, as far as is yet known, no specific diagnostic criteria, is of the utmost value as an aid to diagnosis both in preparalytic and in abortive cases."

Fraser (F 61) reported the results of a study of 362 spinal fluids in 126 cases of acute poliomyelitis. This study included the fluids already reported by Peabody, Draper and Dochez, and followed essentially the same technic, except that the cells were more carefully differentiated. He stated that by the method of staining used "the cells were obtained well spread out and in an apparently undamaged condition." He described the cells as follows: "The most common type of cell was the lymphocyte,—large, small, and intermediate. Almost all the cells in the fluid might be of this type. Large mononuclear cells with cytoplasm that was relatively more basophilic and a regular or an irregular or sometimes even a lobed nucleus were always present and might account for at least half the cells. Polymorphonuclear cells were usually absent, but were present in all the fluids obtained on the second day of the disease and in 80 per cent of those obtained on the third day. The average differential count of these cells was 34 per cent on the second day and six per cent on the third. Endothelial cells like those seen in smears from the surface of the meninges were rare. In every fluid degenerating cells were found that showed no cytoplasm or only ragged shreds of cytoplasm and a nucleus that was breaking down. These cells were probably mononuclear in type, but classification was usually impossible. They were present in some fluids to the extent of 20 or 30 per cent. A few plasma cells could also be identified in some of the fluids. In the more acute stages large cells with very irregular nuclei and a faintly basophilic and vacuolated cytoplasm were present in considerable numbers. Large phagocytic cells were very rare."

The epidemic of poliomyelitis in 1916 furnished material for numerous studies on the spinal fluid in this disease. A review of all of these studies would add little of value, as in the main they only confirm the fact already established.

The first reference to the use of colloidal gold reactions in the study of spinal fluids from cases of poliomyelitis was made by Johnston in 1916 (J 11). He stated that "six fluids from four patients with acute anterior poliomyelitis were examined. Four of these, one from each patient, at the first examination caused a reduction of the colloidal gold in the



so-called syphilitic zone. Two of these showed pleocytosis and three gave positive globulin tests. . . . This occurrence of an early transitory reaction in the syphilitic zone in the acute stage of anterior poliomyelitis suggests an important aid in the diagnosis of this disease."

In a later article by Jeans and Johnston (J 1b) the results of colloidal gold tests with fluids from 100 cases of poliomyelitis were reported. In fluids from undoubted cases of poliomyelitis there was a reduction of the colloidal gold solution with the lower dilutions, the curves ranging from 1123321000 to 1121000000. This reduction occurred even in instances where there was no increase in globulin by the Noguchi test and no increase, or a very slight increase, in the cell count. The same type of curve was found in spinal fluids taken in the preparalytic stages of the disease and in nonparalytic forms. They stated that: "A Lange reaction is good evidence that a spinal fluid is pathologic and is sufficient to differentiate between poliomyelitis and meningism or any other condition giving a normal cerebrospinal fluid. . . . From these results it is to be concluded that the colloidal gold reaction is of distinct service in the diagnosis of poliomyelitis. The greatest usefulness of the reaction is in showing to be pathologic a fluid which does not give other evidence of abnormality when examined as to its albumin, globulin and cellular content. This evidence of abnormality is most useful in those cases of poliomyelitis in which there are the usual symptoms of onset and in which paralysis has not developed. It is our belief that the Lange reaction is of service in differentiating between poliomyelitis and tuberculous meningitis, between which diseases there not infrequently arises for a time a confusion as to diagnosis."

Neal, Abramson, and associates (N 3) reported findings in cytology and chemistry essentially in accord with those already described. The differential count of mononuclears and polymorphonuclears deserves attention. In a series of 2000 fluids, the polymorphonuclears predominated in only 39 instances: 4 on the second day; 6 on the third day; 1 on the fourth day; 5 on the fifth day; 3 on the sixth day; 7 on the seventh day; and others up to the twenty-seventh day. They believed, therefore, that the polymorphonuclear cells represented a type of reaction—not a stage of the disease.

They also state that in a few cases the fluid findings are within normal limits.

The possibility that products of degeneration in the spinal fluid in cases of poliomyelitis might give rise to a nonspecific Wassermann reaction was proved not to be true by consistently negative reactions

in about 350 spinal fluids. The Wassermann tests were done by Miss M. A. Wilson.

A study was made of the colloidal gold curves in 114 spinal fluids in poliomyelitis. These were compared with the curves of fluids from cases of meningism, tuberculous meningitis, and meningococcic meningitis.

Seventy-seven fluids from cases of poliomyelitis fell into 1 of 6 types of curves as follows:

|                 | <i>Number<br/>of cases</i> |
|-----------------|----------------------------|
| 1122100000..... | 40                         |
| 1123210000..... | 8                          |
| 1112210000..... | 6                          |
| 1121100000..... | 5                          |
| 1111000000..... | 14                         |
| 1121000000..... | 4                          |

The other 37 fluids had various curves which on the whole closely corresponded to these. The authors made the following statement:

“Every poliomyelitis fluid examined gave a curve falling in one of these six groups, or approximately so, but this cannot be taken to be of absolute diagnostic value, since a few fluids from patients with epidemic and tuberculous meningitis also fell in these groups. Of perhaps greater value is the differentiation of a poliomyelitic fluid, with a practically normal chemistry, and that of meningism. In only one instance was the fluid from a patient with poliomyelitis negative, even with a practically normal chemistry, while the curves from patients with meningism have been negative even with a slightly increased chemistry. Not enough fluids from patients with meningism have been as yet examined to enable us to feel sure that the fluids from them are always negative. If this proves to be true, the gold chlorid curve will be of great value in differentiating poliomyelitis fluid with slight chemical changes from fluids of meningism.”

The laboratory work on colloidal gold curves was done by Miss Georgia Cooper.

Quantitative chemical studies on spinal fluids from poliomyelitis and other diseases were carried out by R. L. Kahn. The determinations included total nonprotein and urea nitrogen, creatin, creatinin, and sugar. The maximum and the minimum of these substances are shown in the following summary:



|                          | <i>Number of<br/>Fluids</i> | <i>Variation per 100 cc<br/>mgm.</i> |
|--------------------------|-----------------------------|--------------------------------------|
| Total nitrogen.....      | 24                          | 16.37 -34.00                         |
| Nonprotein nitrogen..... | 16                          | 8.91 -24.78                          |
| Urea nitrogen.....       | 17                          | 5.06 -26.6                           |
| Creatinin.....           | 22                          | 0.273- 0.609                         |
| Creatin.....             | 11                          | 0.190- 0.495                         |
| Sugar.....               | 36                          | 25.00 -106.3                         |

Practically all spinal fluids in poliomyelitis show a normal or high sugar content. It was found in 3 instances that the sugar content was low. Whether this was due to an error in technic or was an unusual finding, it is difficult to say. In rare instances in other conditions a spinal fluid, normal in other respects, shows a low sugar content.

Felton and Maxey (F 9) published a study of 57 fluids withdrawn from poliomyelitis patients at various stages of the disease. In addition to the cell count and globulin estimation, Wassermann and colloidal gold reactions were determined.

They state their results substantially as follows:

In the acute stage of poliomyelitis, the spinal fluid reacts with colloidal gold in dilutions of from 1:40 to 1:160, producing a maximal decoloration of 3 ("blue"). In the second and third weeks the reaction is practically the same as in the acute stage but the findings are not constant. Some fluids show a tendency to clear up, others show a precipitation in the higher dilutions. From the fourth to the eighth weeks the reaction runs practically parallel to the globulin-albumin content, persisting in some cases to the eighth week and beyond, but still occurring in dilutions of from 1:40 to 1:160.

Since the reaction is constant in the same zone, the authors conclude that it is helpful in the diagnosis of poliomyelitis.

Kolmer, Freese and associates (K 22) reported the results of cytological and chemical examinations of a large number of spinal fluids withdrawn in most cases at varying periods of time after the onset of paralysis. Their results agreed with those already reported. They also carried out the colloidal gold reaction with 38 fluids collected from 2 to 19 days after paralysis had developed. In 18 instances there was no color change at all, and in 4 there was only a slight precipitation in the first 2 tubes. The remaining 16 fluids yielded reactions of either the "luetie or meningitic zone" type. In more than half the fluids tested therefore the colloidal gold reaction was within normal limits.

Three tests which are not generally used were carried out by this group of workers:

1. *The Mayerhofer Potassium Permanganate Reduction Reaction.* This was employed in the study of 78 spinal fluids. The reduction index was found to vary from 0.7 to 6.1. In 32 instances the index was more than 2.4. An index of more than 2.3 is regarded as indicating an increased protein content. This test has no apparent advantages over a quantitative protein determination.

2. *The Weil-Kafka Hemolysin Reaction.* Under normal conditions antishoop hemolysin and hemolytic complement are not found in spinal fluid. Tests were made for the antishoop hemolysin in 65 poliomyelitis fluids and for both substances in 43 fluids, with positive findings in 66 and 30 per cent respectively. These results indicated an increased permeability of the meningeal vessels in poliomyelitis.

3. *Hauptmann's Saponin Reaction.* Solutions of saponin hemolyze erythrocytes. In certain diseases of the central nervous system the spinal fluid may contain a substance, supposed to be cholesterol due to degenerating lesions, which inhibits this hemolysis. This inhibiting action was not found in the spinal fluids from 30 cases of acute poliomyelitis.

The authors conclude: "A definite and absolute diagnostic criterion or laboratory test with the cerebrospinal fluid in acute anterior poliomyelitis has not been discovered. A clear or slightly opalescent fluid flowing under increased pressure, sterile as examined by smear and culture when collected aseptically, poor in fibrin, reducing Fehling's solution and containing an increased number of cells chiefly of the mononuclear variety, are the most constant findings. An increase in protein and a high potassium permanganate reduction index strengthen the diagnosis, while a colloidal gold reaction of the luetic and meningitic zone types and the presence of natural antishoop hemolysin are helpful diagnostic data."

Larkin and Cornwall (L 15) reported the study of a fairly large number of spinal fluids of acute poliomyelitis. It is interesting to note that in the fluids of the first to the fourth day of the disease, the lymphocytes predominated—92.6 per cent being the average—and that in the later stages the percentage of polymorphonuclears increased, averaging 25 per cent in a small number of fluids withdrawn from the tenth to the fifteenth day of the disease. The colloidal gold reaction was done with 50 fluids at various stages. The curves were of different types so that the authors concluded that there was no curve diagnostic of poliomyelitis. The most common curve, however, was 1111000000, and in the majority of instances, as has been noted by other observers, precipita-



tion took place in the lower dilutions. The authors noted that there was no parallelism between the colloidal gold curve and the other spinal fluid or blood findings.

Regan and Cheney (R 3) published the results of the colloidal gold reaction with 74 fluids from 21 patients at different stages of poliomyelitis. They state that in no instance was the colloidal gold reaction normal in the first 3 weeks of the disease and that it was constantly in the same zone, essentially 1122110000. As the disease progressed, the curve gradually fell but it reached normal in the eighth or ninth week in only about a third of the cases. The authors believed that there was a relationship between the duration of the positive colloidal gold curve and the acute inflammatory stage of the disease. The colloidal gold curve was uniformly negative in the spinal fluids from cases of meningism. The authors thought that the colloidal gold curve was the most valuable laboratory method for the diagnosis of poliomyelitis.

A further study was published by Regan, Litvak and Regan (R 4) in which the colloidal gold test was made on 132 spinal fluids from 42 patients with essentially the same results and conclusions.

Dickie (D 12) reported the total and differential cell count of spinal fluids on different days of the disease. Eighteen fluids were examined on the first day, with cell counts ranging from 8 to 1040. In 11 instances the lymphocytes constituted 50 per cent or more of the cells. This would indicate that even in the earliest stages a preponderance of lymphocytes occurs quite as often as a preponderance of polymorphonuclears. On practically every day an occasional fluid was found in which there was an excess of polymorphonuclears and in the counts of 21 fluids examined on the ninth day or later there were 3 instances in which the polymorphonuclears were 80, 85, and 100 per cent respectively. This corroborates our own observations in 1916.

Lyon (L 74) studied the spinal fluids in 3 cases of poliomyelitis before and after the development of paralysis. In the preparalytic stage the cell counts varied from 900 to 1200 and the proportion of multilobed cells from 59 to 63 per cent. These counts were made immediately following the withdrawal of the fluid. Portions of the fluids were kept at room and at incubation temperature and counts were made at intervals of from  $\frac{1}{2}$  to 12 hours. It was found that the cell count, particularly of the multilobed cells, fell off rapidly, owing, the author thought, to some cytolytic factor which acted upon the multilobed cells more than upon the mononuclear cells. When paralysis developed the cells in the spinal fluids decreased in number and became almost entirely of the mononuclear type.

It has already been stated that other observers have not confirmed the finding of polymorphonuclear cells in the preparalytic period with any degree of regularity.

Thelander, Shaw and Limper (T 7) found that the cell count in most cases of poliomyelitis was between 50 and 200. In their series of 122 cases, a cell count below 50 was found in 19.7 per cent. In regard to low cell counts the authors state: "it has been our experience that bulbar or cerebral cases, without marked clinical involvement of the cord, often show a low count. . . . On the other hand, if, with bulbar signs, the cord also is extensively involved, the count may be high. The number of cells apparently is more dependent on the location of the pathologic process in relation to the meninges than on the stage of the disease."

A polymorphonuclear percentage over 50 was found in almost half of their cases, but there was no marked drop in this percentage during the first 5 days of the disease.

In this series a preponderance of polymorphonuclears over lymphocytes was found in a larger percentage of cases than usual. The authors suggest that this may be accounted for by variations in different epidemics and by the technic of staining and studying the cells.

During the epidemic of 1931 in New York City, many spinal fluids were examined in the laboratory of the meningitis division of the Health Department. Data on certain of the fluids withdrawn by the clinicians of the division have been analyzed by Ruth Gosling. Of 271 fluids withdrawn during the first 72 hours, when there was no paralysis, a preponderance of mononuclears of 75 per cent or more was found in 231 fluids. In only 40 was there 25 per cent or more of polymorphonuclears. In 6 other fluids withdrawn from the fourth to the eighth day of the disease, there was 25 per cent or more of polymorphonuclears. These fluids were sent immediately to the laboratory for examination, and in the great majority of instances not more than an hour elapsed after the puncture was done until the cells in the spinal fluid were counted. These figures show clearly that in this epidemic at least the early stage of the disease was not characterized by a polymorphonucleosis in the spinal fluid.

A brief résumé of the spinal fluid findings in poliomyelitis may be given as follows.

In rare instances the spinal fluid may be within normal limits.

In the great majority of cases, early in the disease there is an increase in cells, varying from slightly above normal to a thousand or more. Usually these cells show a high preponderance of mononuclears. Occa-



sionally there may be polymorphonuclears, 50 per cent or more. The presence of polymorphonuclears is not necessarily limited to the early stages of the disease, and it probably indicates a type of reaction. As there is a little difference of opinion in regard to the occurrence and significance of the polymorphonuclear cells, further study of the cytology is needed. The cells should be counted immediately after withdrawal, and care should be used in preparing and staining the smear. The fluid should be kept from 12 to 24 hours and examination of the cytology made at intervals to determine whether or not in poliomyelitis disintegration of the cells speedily takes place.

The protein shows a slight to moderate increase. There is no parallelism between the increase in cells and the increase in protein. Some fluids show a high cell count with a normal or slightly increased protein; others a normal or slightly increased cell count with a greater increase in the protein.

The cell count usually falls to normal at the end of about 2 weeks. The increase in the protein may remain up to the seventh or eighth week.

The sugar content is normal or high.

Colloidal gold curves quite regularly show a change in the lower dilutions, 1122100000 to 1123321000 being the characteristic curves. Further study of colloidal gold curves is indicated as it has been suggested that fluids from cases of poliomyelitis with no protein increase give changes in a colloidal gold curve, while spinal fluids from cases of meningism with a slight protein increase show a normal curve.

Routine laboratory studies, except for the examination of the spinal fluid, are of little value in the diagnosis of poliomyelitis. Testing the power of the serum to neutralize the virus is too time-consuming and expensive to permit of its general use. The same statement may be made in regard to efforts to determine the presence of the virus in the nasopharynx or intestinal tract. The technic and the value of these tests are described elsewhere in the text.

Studies of the colloidal gold reaction of the serum of patients and laboratory animals have been made by Eberson (E 3) and by Eberson and Mossman (E 4) with a view to determining by this test the presence of immune bodies. The work is still in the experimental stage. It is described elsewhere in the text.

Certain laboratory and Roentgen-ray examinations are at times necessary in the differential diagnosis of other diseases which may be confused with poliomyelitis. Reference will be made to these examinations in discussing differential diagnosis.

The blood count in poliomyelitis has been studied very extensively. No attempt has been made to review the many references in the literature.

One of the earliest reports of blood counts is given by Eduard Müller (M 51), and is an exception to the general rule. He found in the majority of a small group of cases a leucopenia, 3000 to 5000 leucocytes with a slight increase of the lymphocytes.

In the same year La Fetra (L 2) reported in 6 cases a leucocytosis running from 13,400 to 20,600.

Gay and Lucas (G 5) found the following counts in 4 patients:

Case I. Fifth day of the disease: White blood cells, 17,400; lymphocytosis.

Case II. Second day of the disease: White blood cells 10,000; 62 per cent lymphocytosis.

Case III. Fourth day of the disease: White blood cells, 12,000; normal differential count.

Case IV. Fourth day of the disease: White blood cells, 13,400; 75.5 per cent polymorphonuclears.

Peabody, Draper and Dochez (P 7) published a very complete and detailed study of blood counts in patients of different ages and at different times during the early stages of the disease. In the first week the leucocyte count varied from 12,200 to 24,600; in the second week, from 12,000 to 24,500; in the third week from 10,400 to 23,300; in the fourth week, from 11,600 to 20,300. In counts done on 6 preparalytic or nonparalytic cases the earliest count varied from 8800 to 35,600.

In the differential counts, there was an increase of 10 to 15 per cent in the polymorphonuclears. The number of leucocytes and the percentage of polymorphonuclears was often higher in the second or third week than in the first week of the disease. There was an increase in the leucocytes and in the percentage of polymorphonuclears as late as the seventh week.

Larkin and Cornwall (L 15) published the following summary of blood counts:

|                                   | <i>Number</i> | <i>Average<br/>Total<br/>Leucocytes</i> | <i>Polymorpho-<br/>nuclears<br/>per cent</i> |
|-----------------------------------|---------------|-----------------------------------------|----------------------------------------------|
| First to fourth inclusive.....    | 22            | 16,000                                  | 46                                           |
| Fifth to ninth inclusive.....     | 4             | 21,000                                  | 65                                           |
| Tenth to fifteenth inclusive..... | 3             | 11,000                                  | 78                                           |

They concluded that the leucocytes reached the greatest number from the fifth to the ninth day and that the lymphocytes predominated



during the first days of the illness and diminished as the disease progressed.

As the ages of the patients are not given it is difficult to draw too definite conclusions from these figures as the normal differential count varies so greatly in the earlier years of life.

Dickie (D 12) reported leucocyte counts in 14 cases from 1 to 16 days after onset. The total white count varied from 8300 to 26,750 and the percentage of polymorphonuclears from 35 to 87 per cent. The ages of the patients were not given. In this series of cases there seemed to be no tendency for the leucocytes or the percentage of polymorphonuclears to increase after the first few days of illness. Five patients in this group died. The blood counts in these fatal cases differed in no way from those in patients who recovered.

Thelander, Shaw and Limper (T 7) state that: "slight leucocytosis with a relatively high polymorphonuclear count was fairly characteristic. Exceptions occurred. In a few cases a high count up to 20,000 or 30,000 was encountered, and in a few others counts below 10,000 or even distinct leucopenias, but even in these the polymorphonuclear percentage was relatively high."

A review of these reports indicates that there is a varying degree of leucocytosis with an increase in the percentage of polymorphonuclears, which begins at the onset in poliomyelitis and lasts in some instances for 4 to 6 weeks. It is obvious that such a blood picture is of relatively little value in diagnosis.

### DIFFERENTIAL DIAGNOSIS

The problem of the differential diagnosis of poliomyelitis must be considered from two angles; first, the diagnosis of nonparalytic cases and those in the preparalytic stage; and secondly, the diagnosis of cases with paralysis. The history, the clinical examinations, and the spinal fluid findings will usually establish the diagnosis.

The importance of a careful history can hardly be over-emphasized. With an accurate history the physician is less likely to diagnose as acute poliomyelitis a case with a febrile attack which has some neurological condition of long standing, or congenital spastic paralysis, amaurotic family idiocy, mental deficiency accompanied by motor phenomena, or an old poliomyelitis. A normal spinal fluid examination will almost definitely rule out the possibility of an acute poliomyelitis superposed upon an older neurological lesion.

## PREPARALYTIC OR NONPARALYTIC CASES

In the preparalytic stage or in the nonparalytic type of case, poliomyelitis must be differentiated chiefly from the following groups of diseases.

**I. Acute Infections of the Central Nervous System**

**Meningococcic Meningitis and Other Purulent Forms of Meningitis.** In the symptoms of onset and the early clinical picture these may closely resemble poliomyelitis. A herpetic eruption is fairly common in meningococcic meningitis and very rare in poliomyelitis. A hemorrhagic eruption of different types is found in a varying proportion of cases of meningococcic meningitis, occasionally in the other purulent forms, and not at all in poliomyelitis. The examination of the spinal fluid and the demonstration of the infecting organism will establish the diagnosis of the type of meningitis. If the organism cannot be demonstrated a low spinal fluid sugar will rule out poliomyelitis and indicate that the disease is meningitis. It may occasionally happen that more than one spinal fluid must be examined before the diagnosis is established.

**Tuberculous Meningitis.** The onset is usually sudden in poliomyelitis and slow in tuberculous meningitis, but in each disease a few cases depart from the rule. The early symptoms and physical signs in these exceptional cases may not be dissimilar. The spinal fluid examination in early tuberculous meningitis may resemble that of poliomyelitis, as at that stage the tubercle bacillus is difficult or impossible to demonstrate and the spinal fluid sugar may be normal. A fibrin web quite constantly forms in the fluid in tuberculous meningitis and occasionally in poliomyelitis. Repeated spinal fluid examination may, therefore, be necessary before the diagnosis is made. A tuberculin test and a Roentgenogram of the chest may assist in the diagnosis.

**Acute Syphilitic Meningitis.** This problem in differential diagnosis is extremely rare, but the possibility of a syphilitic involvement must not be forgotten in cases suspected of being poliomyelitis but presenting atypical symptoms. In such instances a Wassermann of the blood and spinal fluid should be made. If a patient who is known to have syphilis develops an acute febrile attack, with or without paralysis, especially during an epidemic of poliomyelitis, it may be difficult or even impossible to decide immediately whether he is suffering from poliomyelitis or from cerebrospinal syphilis.



**Epidemic Encephalitis.** The clinical picture of epidemic encephalitis is often more bizarre than that of poliomyelitis and the onset is usually more gradual. But it may be safely stated that the differential diagnosis of the ataxic and encephalitic forms of poliomyelitis, and even of the nonparalytic type from epidemic encephalitis cannot be made with absolute certainty. The changes that take place in the spinal fluids in the two diseases cover about the same range and afford no reliable help. If the course of the disease is prolonged for more than 2 or 3 weeks, we may be reasonably sure that it is encephalitis, but the acute stage of encephalitis may be of short duration. In times of epidemics of poliomyelitis, we do not hesitate to make the diagnosis of the nonparalytic and even of the ataxic and encephalitic types of the disease. In nonepidemic times, and especially in the winter, when poliomyelitis is less likely to occur, we are much less certain of our diagnosis.

These statements also apply to encephalitis following acute infections, vaccination, etc. Indeed it may be that these forms of encephalitis are closely allied to epidemic encephalitis.

**II. Meningism.** Signs of meningeal irritation, closely resembling the early neurological signs of poliomyelitis, occur in the early stages of many diseases, especially pneumonia, gastro-enteritis, dysentery, acidosis, tonsillitis, retropharyngeal abscess, influenza. The diagnosis of pneumonia can be made on the physical signs, but sometimes 2 or 3 days will elapse before this is possible. In influenza, the characteristic leucopenia is a valuable aid in diagnosis. The spinal fluid in all these conditions is usually increased in amount but otherwise normal.

**III. Serous Meningitis.** This may occur with otitis media, mastoiditis, sinusitis, or brain abscess. The presence of the underlying infection usually makes the diagnosis clear. In some instances, however, there may be difficulty in establishing a diagnosis of sinusitis or brain abscess until Roentgenograms have been made. The spinal fluid in serous meningitis usually shows a higher cell count than is the rule in poliomyelitis and there is a preponderance of polymorphonuclears, which may, however, occur also in poliomyelitis.

During an epidemic the diagnosis of poliomyelitis is often feared and suspected in cases in which under ordinary circumstances a careful clinical study with laboratory tests would reveal the true diagnosis without the question of poliomyelitis arising. In other words, during an epidemic many physicians approach almost every patient with the attitude "Has he poliomyelitis?" instead of "What disease has he?"

This is illustrated by the following case which I was called to see in the fall of 1931. The family physician suspected poliomyelitis because the patient, an adult, had fever, gastro-intestinal disturbances, and some stiffness of the back. The history revealed the fact that several days before the onset of symptoms, the patient and a friend had eaten at a restaurant. The friend developed many similar symptoms at the same time. Furthermore, the patient had shown, shortly before I saw him, a moderate degree of puffiness around the eyes. A diagnosis of trichinosis was therefore suggested, which was confirmed at the hospital to which the patient was admitted.

#### PARALYTIC CASES

After paralysis has developed the diagnosis of poliomyelitis is usually easier than in those cases without paralysis. But even in these instances there are numerous diseases and conditions that must occasionally be considered.

**I. Difficulty in motion or loss of power** due to trauma, such as fractures or sprains, or temporary paralysis due to pressure on a nerve.

The history of an injury, the absence of constitutional symptoms, and a careful physical examination, perhaps with the additional aid of a Roentgenogram, should establish the diagnosis without recourse to lumbar puncture.

#### II. Difficulty in Motion Caused by a Painful Joint

**Acute Rheumatic Fever.** The constitutional symptoms may suggest poliomyelitis and there is not infrequently pain on movement of the joint before the swelling takes place. The neurological signs of poliomyelitis are lacking. An endocarditis or a pericarditis will lend weight to the diagnosis of rheumatic fever, as will also the localization of hyperesthesia and pain in the joints rather than along the nerve trunks. The early appearance of swelling in the joints will often make a lumbar puncture unnecessary.

**Serum Sickness Involving the Joints.** In this condition there is usually fever and often vomiting. A history of an injection of serum, and an urticarial rash will enable the diagnosis to be made. Swelling of the joints will occur later.

**Tuberculosis of the Joints or Spine.** There may be restriction of motion due to pain, or paralysis due to pressure on the nerves. The diagnosis will be established by the history of a gradual onset and a careful physical examination, with Roentgenograms. A positive tuberculin skin test is helpful.



### III. Pseudo-paralyses

**Rickets and Scurvy.** A careful physical examination will show other signs and symptoms of these two diseases. A Roentgenogram and the indicated laboratory tests of the blood and urine (for hematuria, for scurvy) will confirm the diagnosis.

**Syphilitic Periostitis or Osteitis.** The diagnosis will be made by finding other syphilitic lesions and by a Wassermann test and X-ray.

**Osteomyelitis.** A careful examination of the paralyzed limb will usually reveal the lesions. A Roentgenogram will aid in the diagnosis. The constitutional symptoms may be somewhat similar, but the temperature curve in osteomyelitis usually suggests a septic process and the neurological symptoms of poliomyelitis are usually lacking.

### IV. Paralyses of Other Types

**Transverse Myelitis.** The loss of sensation below the lesion and the involvement of the bowels and bladder easily establish the diagnosis of transverse myelitis. The reflexes may be lost immediately after the onset of paralysis but in a short time they are increased.

**Peripheral Neuritis.** This may be toxic from various poisons such as lead, arsenic, or alcohol. In this form, the fever and constitutional symptoms of poliomyelitis are lacking. The paralysis is usually symmetrical and develops more slowly than in poliomyelitis. A careful history will usually reveal the etiological agent, and in the case of lead and arsenic, laboratory tests for these substances are of assistance.

Post-diphtheritic paralyses usually appear several weeks after an attack of diphtheria. The history of a sore throat from 2 to 4 weeks earlier is therefore important. The development of the paralyses is usually slow and the soft palate and muscles of accommodation are almost invariably involved. Ordinarily constitutional symptoms are lacking. A peripheral neuritis may follow other acute infections. In all forms of peripheral neuritis the spinal fluid is essentially normal.

**Bell's Palsy.** The absence of constitutional symptoms and a normal spinal fluid will rule out poliomyelitis.

**Paralyses in Meningitis.** Although paralyses may develop in the various forms of purulent meningitis, the question of poliomyelitis under these conditions is not likely to arise, as the examination of the spinal fluid should reveal the infecting organism.

In the case of syphilitic meningitis, however, the diagnosis may oc-

asionally be in doubt until a Wassermann test of the spinal fluid has been made.

In tuberculous meningitis the problem may be more difficult, as early in tuberculous meningitis the spinal fluid findings may closely resemble those of poliomyelitis. The paralyses in tuberculous meningitis are more likely to be transient and migratory than is the case in poliomyelitis. Eventually the examination of the spinal fluid will reveal a low sugar content and the tubercle bacilli.

**Paralysis from Various Causes.** The paralyses that occur in connection with brain tumor, brain abscess, and cerebral thrombosis or hemorrhage will rarely be confused with poliomyelitis. In the case of emboli, especially from endocarditis, there is occasionally some confusion in diagnosis. A febrile and constitutional reaction is present. The spinal fluid may show early a larger number of cells and a higher percentage of polymorphonuclears than is usually the case in poliomyelitis, but there are enough deviations from the rule to make this not particularly helpful. If the heart lesion is obviously becoming more serious, it is an argument in favor of an embolus, but unless the patient has been under very careful observation, there will be no exact information in regard to the progress of the lesion of the heart. If the paralysis is due to an embolus it will become spastic in type after a few days. In unfavorable cases more emboli will be thrown off. It will often be necessary to study the case for a time before arriving at a definite diagnosis.

In this discussion no effort has been made to take up all the differential points. It has seemed necessary merely to refer to the more common diseases and conditions that must be borne in mind when attempting to diagnose a case possibly suffering from poliomyelitis and to mention a few details that may be helpful. If we are frank, we must admit that in a certain number of cases the diagnosis will be a matter of opinion, and in that we may err. After all, upon what can we make a definite diagnosis of poliomyelitis? Not upon the spinal fluid examination. For the spinal fluid may be within the accepted normal limits in a small number of cases that clinically are poliomyelitis. Moreover, the changes that usually occur in the spinal fluid in poliomyelitis are by no means pathognomonic. They are found also in encephalitis, early in tuberculous meningitis, in brain tumor, and also, under certain conditions, in various acute infections. The diversity of the clinical manifestations and their similarity to those found in other diseases have already been emphasized. Therefore in the more atypical cases an



absolute diagnosis would rest on the examination at necropsy in fatal cases or upon the slender chance of demonstrating the virus in the washings of the mucous membrane of the nasopharynx as was done by Paul.

## PROGNOSIS

The prognosis in poliomyelitis presents several problems: (1) the prognosis as to life; (2) the probability that paralysis may develop; (3) the degree of restitution of function that may be expected if paralysis occurs.

All figures on the case fatality in epidemics and especially in inter-epidemic periods are probably too high on account of the failure to diagnose nonparalytic and abortive cases. An interesting observation, illustrating this point has been made by Dr. Frank W. Laidlaw. This excerpt is taken from a paper read by Dr. Laidlaw at the meeting of the American Medical Association in New Orleans, May, 1932.

"The fatality rate of the 1931 outbreak was the lowest recorded in the state. With 2051 cases reported, 164 deaths occurred,—a fatality rate of 8.0 per cent. This is a striking reduction from that of the 1916 outbreak with 4215 cases and 901 deaths,—a fatality rate of 21.4 per cent.

"In 1930 there were 660 cases reported in the state, exclusive of the city of New York, with 111 deaths,—a fatality rate of 16.8 per cent.

"This reduction is more apparent than real. The utilization of better methods of diagnosis and closer observation of cases resulted in a far greater number of reports.

"In 1916 only paralyzed cases were reported. In 1931, 57 per cent of the cases were in the preparalyzed stage at the time of diagnosis and report. In 1930, approximately 18 per cent were in the preparalytic stage when reported.

"The revision of the figures for 1916 and 1930 on the basis of 1931, shows a striking similarity in fatality rates:

|      | <i>Cases</i> | <i>Deaths</i> | <i>Fatality Rate</i> |
|------|--------------|---------------|----------------------|
|      |              |               | <i>per cent</i>      |
| 1916 | 4,215        | 901           | 21.4                 |

Probably all paralyzed cases. 1931, 43 per cent of reported cases were paralyzed. If this same proportion held in 1916, the figures might be revised as follows:

|      | <i>Cases</i> | <i>Deaths</i> | <i>Fatality Rate</i> |
|------|--------------|---------------|----------------------|
| 1916 | 9,790        | 901           | 9.2                  |
| 1930 | 660          | 111           | 16.8                 |

Approximately 82 per cent of these 1930 cases were reported as paralyzed. The figures might be revised to correspond with 1931 figures as follows:

|      |       |     |     |
|------|-------|-----|-----|
| 1930 | 1,259 | 111 | 8.8 |
| 1931 | 2,051 | 164 | 8.0 |

Note the fatality rates: 1916, 9.2 per cent; 1930, 8.8 per cent; 1931, 8.0 per cent."

The entire question of case fatality is fully discussed in the *Chapter on Epidemiology*. It is sufficient to note here that it ranges from 5 to more than 40 per cent. It is impossible to state a fair average on account of the different proportions of nonparalytic cases reported in different epidemics. Age has an important influence on case fatality. In the first year of life it is generally high. From the first to the tenth year it is low. After the tenth year there is a gradual increase with the increase in age.

In considering the individual patient, the probability that paralysis will develop and the prognosis as to life are definitely related, as recovery is almost invariably certain unless there is paralysis. Various estimates are given of the proportion of paralyzed and nonparalyzed cases. Draper (D 18) writes: "... all observers agree that they (the non-paralyzed cases) represent at least 50 per cent of the total incidence of the disease, and some place the figure as high as 70 to 80 per cent." Wickman gives estimates of "abortive" cases as 35 to 56 per cent and suggests that under certain conditions the frequency may be greater. In a group of nearly 500 cases studied in the early stage in the 1931 epidemic in New York City, and checked by examination of the spinal fluid, paralysis failed to develop in approximately 75 per cent of cases although no serum treatment was given in these cases.

The clinical indications that point to a favorable or unfavorable prognosis in a given case in the early stage are unreliable. The symptoms of onset may be quite as severe in the cases that do not go on to paralysis as in those in which extensive paralysis develops. Wickman writes: "Can we from any clinical data predict the course and termination of the disease in a given case? All clinicians agree that the intensity of



the initial symptoms has no prognostic significance. Alarming initial symptoms may usher in a benign or an abortive attack; and a mild beginning may be the prelude of a stormy, perhaps of a fatal course." Ruhräh and Mayer (R 58), Peabody, Draper and Dochez (P 7) and others agree with this statement.

TABLE 5  
DEVELOPMENT OF PARALYSIS IN CASES SHOWING INCREASED CELLS IN SPINAL FLUIDS TESTED IN PREPARALYTIC STAGE OF WHICH 75 PER CENT OR MORE WERE MONONUCLEARS\*

| CELL COUNT | TOTAL FLUIDS EXAMINED | NUMBER DEVELOPING PARALYSIS | PER CENT DEVELOPING PARALYSIS |
|------------|-----------------------|-----------------------------|-------------------------------|
| Up to 50   | 145                   | 38                          | 26                            |
| 50-100     | 77                    | 32                          | 41                            |
| 100-200    | 41                    | 19                          | 46                            |
| 200-500    | 36                    | 20                          | 55                            |
| 500-1,200  | 8                     | 2                           | 25                            |
| Total..... | 307                   | 111                         | 36                            |

\* Gosling (Meningitis Division, New York City Health Department).

TABLE 6  
DEVELOPMENT OF PARALYSIS IN CASES SHOWING INCREASED CELLS IN SPINAL FLUIDS TESTED IN PREPARALYTIC STAGE OF WHICH 25 PER CENT OR MORE WERE POLYMORPHONUCLEARS\*

| CELL COUNT | TOTAL FLUIDS EXAMINED | NUMBER DEVELOPING PARALYSIS | PER CENT DEVELOPING PARALYSIS |
|------------|-----------------------|-----------------------------|-------------------------------|
| Up to 50   | 3                     | 0                           | 0                             |
| 50-100     | 5                     | 1                           | 20                            |
| 100-200    | 14                    | 7                           | 50                            |
| 200-500    | 12                    | 7                           | 58                            |
| 500-1,100  | 4                     | 2                           | 50                            |
| Total..... | 38                    | 17                          | 44                            |

\* Gosling (Meningitis Division, New York City Health Department).

A pulse rate increased out of proportion to the temperature, rapid respirations or extreme prostration are often indications of an unfavorable prognosis, even before paralysis develops. The cell count in the spinal fluid has some bearing on the probability of paralysis developing. Draper (D 18) writes: "The spinal fluid, contrary to the opinion usually held, offers undoubtedly some prognostic suggestions. There are a

sufficiently large number of observations to indicate that cases which show cell counts of less than 100 per c. mm. during the first 12 to 18 hours rarely develop muscular weakness, or at the most a transient facial paresis. Furthermore, cases having cell counts of 200 to 500 very frequently develop paralysis of the severer sort. With few exceptions the fatal cases showed counts of over 700 or a thousand."

Tables 5 and 6 show the percentage developing paralysis in two groups of cases: in Table 5 the 307 cases in which 75 per cent or more of the cells were mononuclears; in Table 6, the 38 cases in which 25 per cent

TABLE 7  
CASES DIAGNOSED AS POLIOMYELITIS IN THE PREPARALYTIC STAGE CLASSIFIED  
WITH REFERENCE TO CELL COUNTS\*

| CELL COUNT PER CUBIC<br>MILLIMETER                      | TOTAL<br>CASES | FINAL OUTCOME                            |               |                |             |             |              | PER CENT<br>OF<br>RECOVERY<br>WITHOUT<br>WEAKNESS<br>OR<br>PARALYSIS |
|---------------------------------------------------------|----------------|------------------------------------------|---------------|----------------|-------------|-------------|--------------|----------------------------------------------------------------------|
|                                                         |                | No<br>weak-<br>ness or<br>paraly-<br>sis | Weak-<br>ness | Paraly-<br>sis | Deaths      |             | Un-<br>known |                                                                      |
|                                                         |                |                                          |               |                | Num-<br>ber | Per<br>cent |              |                                                                      |
| Under 50                                                | 287            | 233                                      | 26            | 24             | 4           | 1.4         | 0            | 81                                                                   |
| 50-99                                                   | 149            | 96                                       | 14            | 31             | 8           | 5.4         | 0            | 64                                                                   |
| 100-199                                                 | 138            | 95                                       | 16            | 15             | 11          | 8.0         | 1            | 69                                                                   |
| 200 and over                                            | 120            | 73                                       | 16            | 21             | 9           | 6.0         | 1            | 61                                                                   |
| No count or no cells                                    | 16             | 13                                       | 1             | 0              | 0           |             | 2            |                                                                      |
| Total.....                                              | 710            | 510                                      | 73            | 91             | 32          |             | 4            |                                                                      |
| Under 10 cells (in-<br>cluded with "under<br>50" above) | 55             | 49                                       | 5             | 1              | 0           |             | 0            | 89                                                                   |

\* Laidlaw (paper read at meeting of American Medical Association in New Orleans, May, 1932).

or more were polymorphonuclears. In all of these 345 cases, lumbar puncture was done in the preparalytic stage, although probably not often in the first 12 to 18 hours. Both series show an increase in the percentage of cases becoming paralyzed, paralleling the increase in the cell counts, except in those few cases with a cell count of more than 500. Here the number of cases is so small that the results are inconclusive.

Comparable results were obtained by Laidlaw in Hudson River coun- ties and Long Island in the summer of 1931. Table 7 is taken from a paper read by Dr. Laidlaw at the meeting of the American Medical Association, May, 1932, in New Orleans.



If paralysis develops, the prognosis as to life depends upon the localization and extent, and these can in no way be forecast. It has already been stated that death is practically always due to complete paralysis of the muscles of respiration or to pneumonia following partial paralysis of these muscles. The use of the respirator has modified the mortality in cases with respiratory paralysis. Reference has also been made to the occasional death that may result from involvement of the cardiac or respiratory centers with little or no paralysis.

The time at which death is most likely to take place is shown in Table 8 taken from Ruhräh and Mayer (R 58).

TABLE 8  
DEATHS FROM POLIOMYELITIS BY DAY OF DISEASE, NEW YORK CITY EPIDEMIC OF 1916\*

|                            | DEATHS | PER CENT |
|----------------------------|--------|----------|
| Deaths on first day.....   | 55     |          |
| Deaths on second day.....  | 179    |          |
| Deaths on third day.....   | 315    |          |
| Deaths on fourth day.....  | 369    |          |
| Deaths on fifth day.....   | 300    |          |
| Deaths on sixth day.....   | 182    |          |
| Deaths on seventh day..... | 110    |          |
| Deaths in first week.....  | 1,510  | 81+      |
| Deaths in second week..... | 211    | 11+      |
| Deaths in third week.....  | 60     | 3+       |
| Deaths after 21st day..... | 67     | 3+       |
| Total.....                 | 1,848  |          |

\* Ruhräh and Mayer (Poliomyelitis in All Its Aspects, Philadelphia, Lea and Febiger, 1917).

Wickman states: "With respect to the danger upon different days of the disease, there is no uniformity. According to Wickman, life is in greatest peril between the third and seventh days, and the fourth is the most fatal day. Leegaard's figures show that death occurred most frequently on the third or fourth day. Ed. Müller affirms further that on the fourth day severe paralysis most often appears. After the lapse of the second or third week, in cases in which the function of the respiratory muscles is seriously impaired by paralysis, life is especially menaced by pneumonia."

After the paralysis reaches its maximum, improvement takes place continuing sometimes for several years. This improvement may go on to complete recovery. The extent to which restitution of function in paralyzed muscles may be expected has been increased in recent years by a better knowledge of proper orthopedic treatment. To quote MacAusland: "In the epidemics in which the cases of complete restoration of function have been noted, the number has been found to vary extensively. Wickman analyzed 530 cases from one to one and a half years after the acute attack, and pronounced 44 per cent cured and 56 per cent paralyzed. Of 212 cases in the epidemic of 1907 in Massachusetts, investigated by Wood, 27 per cent were considered wholly recovered. In the Massachusetts epidemic of 1910, 16.7 per cent complete recoveries were recorded. In other epidemics, the percentage has been as low as 5.3 per cent. In the New York epidemic of 1916, 1233 out of 3441 cases, treated less than two months, were discharged with no visible paralysis, making 32.6 per cent total recoveries.

"As a rule, if complete return of function is to be the result, power will have returned in six months. Complete recovery may take place in the latter part of the first year, or even later, in cases in which deformity has been corrected, and the muscles properly treated. The usual result is not complete recovery of the muscle, but partial recovery with nearly complete restoration of function, a condition that simulates absolute restoration very closely."

The following statements on prognosis as to function are quoted from Jones and Lovett (J 12):

*"Prognosis as to Function.* Unfavorable elements in prognosis of ultimate paralysis connected with the attack seem to be (1) a slow attack with exacerbations and involvement of new muscles lasting over several days, (2) excessive and persistent tenderness lasting for many weeks under proper treatment. A scattered paralysis seems on the whole to have a more favorable prognosis than a complete loss of power below a certain level. In muscles which remain totally paralyzed for six months, the outlook is not good.

*"Spontaneous Improvement.* This begins in most cases in a few weeks. It does not progress rapidly during the existence of acute tenderness and parents should be warned not to expect too much during the tender stage. It is most rapid for the first six months, but continues to be well marked for at least two years, and under favorable conditions probably goes on longer.

*"Prognosis without Treatment.* Without treatment, spontaneous



improvement will occur in nearly all cases at first, after which functional deterioration from fatigue, muscle stretching, and deformity will eventually take place. Many muscles partly paralyzed in the beginning will become totally paralyzed in moderate cases. Finally, a period of stability, generally with some deformity, will be reached, which may not alter except under the influence of increase of weight, illness, gross overuse, or middle age.

*“Prognosis with Treatment.* The outlook for favorable progress under treatment is best in the first six months, next best in the following six, fair in the second year, and limited after the second year. There seems, however, to be no time limit to the benefit to be derived from treatment; a case of one of the writers of twenty-five years’ standing, who had never walked with the feet on the ground, being most satisfactorily treated by braces which enabled her to walk with a cane; and in another case of thirty-six years’ duration, in a few weeks the gluteus medius muscle more than doubled its contractile strength by careful muscle training and restriction of activity.”

*Sequelae.* It is generally accepted that the after effects of poliomyelitis are limited almost entirely to the disability that may remain as a result of the paralysis. It has already been stated that blindness is a rare symptom and that it is usually transitory. There are no references, so far as I know, to deafness or impairment of hearing. It has been pointed out that the mental and moral deterioration and other symptoms described by Strümpell as occurring after the encephalitic type of poliomyelitis suggest that he was probably dealing with epidemic encephalitis. Wickman (W 21) writes: “After an attack of acute poliomyelitis there seems to remain a certain predisposition to other organic nervous affections. A number of instances are known in which a case of poliomyelitis has developed subsequently a chronic spinal cord affection. Usually chronic muscular atrophy; more rarely progressive myopathy appears.” Ruhräh and Mayer (R 58) state: “Comparatively few cases have been actually reported, and one must always allow for the possibility of coincidence.”

In this connection, I have noted in a number of instances epidemic encephalitis developing in patients who had previously suffered from poliomyelitis. During the epidemic of 1931, it also happened that a few patients in the chronic stage of epidemic encephalitis contracted poliomyelitis. MacAusland (M 1) writes: “It is not uncommon to find both infections in the same patient.”

If the prospects for life and subsequent health of mind and body of a

child suffering from poliomyelitis are compared with those of a child suffering from either epidemic meningitis or epidemic encephalitis, the child with poliomyelitis is in at least as favorable a position as the child with epidemic meningitis and in a far more fortunate position than the child with epidemic encephalitis.

In children suffering from epidemic meningitis, the case fatality is about 20 or 25 per cent, being higher than this in the first 2 years of life and considerably lower after the second year. If the child recovers there is danger of deafness; of loss of vision, usually in one eye, in a smaller percentage of cases, and of hydrocephalus. Paralyzes also occasionally develop during meningitis. Mental defects, except in cases with hydrocephalus, are comparatively rare.

In epidemic encephalitis, the case fatality is higher, perhaps 20 to 30 per cent. And of the cases that recover, at least 50 per cent will develop the chronic stage of the disease with the attendant moral, mental, and physical disabilities.

Probably not more than 25 per cent of all cases of poliomyelitis that can be diagnosed develop paralysis. The case fatality is usually from 10 to 15 per cent. As practically all fatal cases are in the paralyzed group, the number surviving with paralysis is much less than 25 per cent of the total number of cases. Of the cases with paralysis a complete restitution of function will take place in a goodly number and a partial restitution in the remainder. There is, so far as we know, no danger of mental defects and there is but slight indication that the child will be more susceptible to other nervous disorders.



## CHAPTER V

# TREATMENT

### PROPHYLAXIS

The prophylaxis of poliomyelitis must be considered from the point of view both of the community and the individual.

Although few patients give a history of contact with a case, it is generally believed that the disease is spread chiefly by carriers and mild cases. Quarantine is therefore advisable, as it is reasonable to suppose that the isolation of patients will reduce the number of carriers. The effect of quarantine will obviously be diminished by the presence of abortive cases which will escape diagnosis.

The period that quarantine should be maintained is open to some discussion as there are no reliable data to show how long the virus may be present in the secretions of the nasopharynx and possibly in the discharges from the intestinal tract. The data available are presented in detail in the *Chapter on Etiology*. The Committee on Communicable Disease Control of the White House Conference (W 18) recommended for patients an isolation period of three weeks from the onset of febrile symptoms; for exposed children and adults in so far as their vocation brings them into contact with children or makes them food-handlers, quarantine for a similar period was advised. Placarding was not recommended.

The danger of carriers and abortive cases makes it advisable that during epidemic times children should not be allowed to mingle in crowds.

In former times gargling with antiseptics was recommended with a view to destroying the virus. This measure is now regarded as harmful, as Amoss and Taylor (A 24) have shown that antiseptics destroy the virucidal power which exists in the normal secretion of the nasopharynx. It is therefore suggested that normal saline should be used. This might serve to wash away any virus that may have been picked up by casual contact with carriers, and it certainly would not be harmful. A healthy condition of the nose and throat probably furnishes some protection against infection by poliomyelitis. Removal of tonsils and adenoids should, however, take place in inter-epidemic times because cases are on record in which poliomyelitis has developed soon after a tonsillectomy.

It is obvious that children should be kept in the best possible health by adequate food, rest, fresh air and sunshine. It is important to avoid fatigue. As the virus remains viable in milk and butter and may possibly cling to other foodstuffs, the use of unwashed or carelessly handled food during an epidemic may well be avoided. Many attempts have been made to find a means to immunize children actively against poliomyelitis, but no safe method has as yet been developed. An account of the experimental work on this problem is given in *Chapter III*.

Passive immunization yields greater promise. The scientific basis for this procedure is described in detail in the *Chapter on Resistance and Immunity*. In brief, monkeys receiving convalescent serum or immune horse serum at the time of inoculation with the virus, or soon after, are protected from the disease. The success attained with the passive immunization against measles is an additional argument for its use.

The use of convalescent serum as a prophylactic measure against poliomyelitis has not been extensive. It is obvious that on account of the low morbidity of the disease, it must be used in thousands of instances before its value can be proved.

Davide (1928, D 6) believes that he was the first to use convalescent serum as a preventive against poliomyelitis. He did this in 1925 in a province in northern Sweden. The total number of persons in the experimental villages was 157. One out of the 73 inoculated, and 14 out of the 84 not inoculated, developed poliomyelitis. The single inoculated patient who developed poliomyelitis was obviously infected already as he became ill within 40 hours after the injection. The disease ran a very mild course. The dose used was 5 cc., injected intramuscularly.

Flexner and Stewart (1928, F 54) and Flexner (1929, F 19) proposed the use of convalescent serum for passive immunization during epidemics. They suggested a dose of 10 cc. for children and 20 cc. for adults, injected subcutaneously, and repeated in from 4 to 6 weeks if the danger of infection continued.

W. H. Park, in papers as yet unpublished, states that at his suggestion several hundred children in and around New York received passive immunization during the epidemic period of 1931 by means of convalescent serum, normal adult blood or serum, or the refined immune horse serum. Among this number only 3 mild cases of poliomyelitis developed.

Park advises 20 cc. of convalescent serum intramuscularly. If the



convalescent serum is not available, normal or adult serum or blood may be used, because it has been shown that the serum of many adults, in some communities at least, possesses a power of neutralizing the virus nearly equal to that of convalescent serum. It is safer to use the blood or serum of 2 or more adults unless the neutralizing power of the serum can be tested. The use of whole citrated blood is somewhat simpler than that of serum, and the amount suggested by Park is 50 cc. The human serum or blood may afford protection for only about 3 weeks, hence the injection should be repeated during an epidemic. A third method of passive immunization is that utilizing refined immune horse serum. As the neutralizing power of this serum is considerably higher than that of convalescent serum, Park advises 10 cc. intramuscularly. As the protection due to the horse serum does not last as long as that given by human serum, the injection will need to be repeated about every 2 weeks. The horse serum has the additional disadvantages of being likely to cause serum sickness and of possibly inducing hypersensitiveness to horse serum.

The passive immunization against poliomyelitis commends itself both from the experimental proofs of its efficacy and from the apparent success thus far obtained in human beings.

## TREATMENT

The general treatment of patients suffering from poliomyelitis differs in no way from that of patients with any other acute infectious disease. Absolute rest in bed, appropriate diet, adequate elimination, and sedatives as indicated for the pain and restlessness are the principal requirements during the febrile stage. As the virus is known to be contained in the secretions of the nasopharynx and may be present in the discharges from the intestine, measures must be taken to avoid infection by these substances and to sterilize them adequately.

Many attempts have been made to avert paralysis or to check its course if it has developed. These may be grouped roughly under three headings: miscellaneous measures; measures to reduce the increased pressure in the subarachnoid space and presumably also the edema of the cord and brain; administration of serum.

### Miscellaneous Measures

Various drugs have been suggested and tried without success. A discussion of most of them would be tiresome and unprofitable. It

may be well to discuss briefly hexamethylenamin, the use of which is frequently referred to in the literature.

This drug has been found to pass into the spinal fluid. Flexner and Clark (F 31) found that in monkeys, when it was given before the virus was injected, and administered by mouth daily thereafter, the incubation period was sometimes prolonged and paralysis occasionally prevented. Hexamethylenamin has therefore been used as a preventive aid in the acute stage of the disease. Later Flexner and Amoss (F 28) reported that they were unable to block the development of experimental poliomyelitis, following intranasal inoculation, by administering the drug by stomach tube.

Fraser (F 62) administered hexamethylenamin orally to 22 patients suffering from poliomyelitis. He concluded, "In no instance did this treatment appear to cut short the acute stage, and in no instance was there evidence of more satisfactory or more rapid recovery in the paralyzed parts." In 2 patients hematuria developed and the urotropin was discontinued.

No data exist showing beneficial effects and the danger of hematuria is always present.

Autotherapy—the subcutaneous or intramuscular injection of the patient's own spinal fluid—was suggested by Duncan (1916, D 30). It was used by Duncan and several other physicians. I can see no rational basis for its use and, judging by its failure to be reported in the more recent literature, it has been apparently discontinued.

The intramuscular injection of the patient's own blood (10 to 20 cc. injected every second day for 10 to 15 doses) was tried in 20 patients during the Rumanian epidemic of 1927. In 10 patients, blood from the mother or father was injected in the same manner. There was apparently no influence on the course of the disease. This treatment was carried out in the early stage of the disease but apparently not in the preparalytic period. It is reported by Manicatide, Brătescu and Rusescu (1929, M 15) and by Marinesco, Manicatide and State-Draganescu (M 19).

Jungeblut (J 16, personal communication), on the basis of encouraging results in the experimental disease in monkeys, tried chaulmoogra oil in a small series of cases at the Willard Parker Hospital in 1931. The treated cases, however, showed no marked improvement as compared with controls.

Kubie has carried out extensive experiments to determine the effect on intracranial pressure and the character of the spinal fluid of intra-



venous injection of hypotonic solutions accompanied by continuous or frequent drainage of the spinal fluid. Two recent articles by Kubie (1928, K 37) and by Retan and Kubie (1931, R 6) are of interest. It has been shown that a greatly increased flow of cerebrospinal fluid may be produced in animals by this method without increasing intracranial pressure or cerebral edema. The same procedure was tried in human subjects without producing any unfavorable results (K 37). It was also shown that "the new cerebrospinal fluid formed under these conditions arose not merely from the choroid plexus but also by transudation through the capillary net-work of the brain and spinal cord" (R 6). It is also stated "that this flow of cerebrospinal fluid, when it occurred in the presence of an inflammation carried with it from the depths of the central nervous system to the surface many products of the inflammatory reaction." Kubie therefore suggests that this method of treatment may be of value in such conditions as purulent forms of meningitis, epidemic encephalitis, and poliomyelitis. He mentions the successful treatment of 1 case of poliomyelitis by Spurling, Louisville, Kentucky (S 51). Retan and Kubie report in detail the use of this method combined with 20 cc. of convalescent serum injected intramuscularly in a second case, which also recovered.

It is obviously impossible to draw any conclusions from the results in these 2 cases. The theoretical considerations are based on a thorough experimental background.

The principal efforts to prevent the development of paralysis in poliomyelitis or to modify its course have, however, proceeded along two lines: attempts to relieve the edema and hyperemia of the tissues of the central nervous system; and attempts to neutralize the virus by convalescent serum or other sera possessing virucidal properties.

### Measures to Reduce Increased Pressure and Edema

The exact pathogenesis of the disease is not known. The early lesions in the experimental disease (Flexner and Lewis, F 47) and in human cases show edema, congestion of the blood vessels, and to a less degree minute hemorrhages. The possible effect of this pressure and also of the resulting anemia on the nerve cells has been emphasized by Peabody, Draper, and Dochez (P 7) and others. On the other hand many workers have believed that the primary action of the virus is directly on the nerve cells, and that the edema and other reactions are secondary. This question is fully discussed in the *Chapter on Pathology*.

Whatever may be the relative importance of these two modes of

action, it is reasonable to assume that the pressure of the congestion and edema and the resulting anemia may have a deleterious effect on nerve cells, whether they are injured or not by the toxic action of the virus.

It is desirable therefore to relieve this pressure if possible. Three methods have been used in an attempt to accomplish this: administration of epinephrin or ephedrin; injection of hypertonic solutions intravenously or by rectum; lumbar puncture.

**Administration of Epinephrin or Ephedrin.** Adrenalin or epinephrin has also been used very extensively. Fraser (F 62) reported its use intraspinally in doses of 1.0 to 310 cc. of a 1:1000 solution in an equal volume of normal saline every 3 to 6 hours. This was tried in 8 cases in which the paralysis was rapidly developing and in which there was extreme respiratory involvement. Following the injection, there was a rise in the systolic pressure of 10 to 20 mm. occurring in from 20 to 30 minutes and disappearing in about an hour. Five of the 8 cases died and Fraser stated that it was impossible to attribute the cessation of the progress of paralysis to the injection in the 3 cases that recovered. This treatment was begun on the basis of work done by Clark (C 12) on the action of epinephrin in experimental poliomyelitis.

Meltzer (M 36) in 1916 strongly advocated the use of adrenalin intraspinally. It was his theory that it would reduce the edema which is one of the early reactions of the tissues of the central nervous system to the invasion of the virus and thereby the nerve tissues in the area would be definitely benefited. Meltzer also suggested "the possibility that the adrenals . . . may be specifically antagonistic to the virus of poliomyelitis." He recommended 2 cc. of a 1:1000 solution intraspinally every 4 to 6 hours, worked in with 2 cc. or more of physiological salt solution. Before the first injection he advised the withdrawal of a fairly large quantity of spinal fluid.

Lewis (L 54) reported the results in 77 cases in which the adrenalin treatment was used in accordance with Meltzer's suggestion. Of these patients 18 died. Of these a number were moribund when treated or died of other conditions. Of the 59 that survived, 21 completely recovered; 21 were greatly improved and it was indicated that quite complete recovery would take place; 17 showed evidence of permanent disability.

Hoyne and Cepelka (H 38) reported that after epinephrin was given intraspinally there was sometimes marked improvement. At times there would be spontaneous movement of a paralyzed arm within an hour after the injection was given. Such marked improvement was



seldom permanent but gradual improvement sometimes seemed to be more rapid."

During the 1916 epidemic in New York (N 20), adrenalin was used intraspinally in 81 cases at Riverside Hospital and in 19 cases at Queensboro Hospital, with death rates of 43 and 52 per cent respectively. Inasmuch as better results were obtained in the untreated cases, the use of adrenalin was discouraged. Weisenburg (W 12) was not convinced of the value of adrenalin and stated that certain cases reacted badly following its use.

In 1930, Brahdy and Scheffer (B 26) published the results in a series of 10 cases of the use of ephedrin intraspinally. Ephedrin is stated to have a more prolonged and less intense vasoconstrictor action than epinephrin, and not to be followed by a secondary vasodilatation. It was used in doses of from 40 to 60 mgm. in 1 cc. of sterile water. The last 2 to 4 cc. of spinal fluid was retained in the gravity apparatus. To this the ephedrin solution was added and the mixture was allowed to gravitate into the spinal canal.

They state that of the 10 cases thus treated 50 per cent died, while of 12 control cases rated as equally severe 75 per cent died.

The authors hesitated to draw definite conclusions from this rather small number of cases but it was their general impression that the effect of the treatment was favorable.

**Injection of Hypertonic Solutions.** The intravenous injection of hypertonic solutions in normal animals has been shown by Weed and his associates (W 8; W 10; W 11; W 9) to result in a reduction of the volume of the brain and spinal cord, a lowering of the pressure of the cerebrospinal fluid, and an aspiration of fluid from the subarachnoid space into perivascular spaces of the brain and cord. Aycock and Amoss (A 39) state that similar results occur in the edematous cords of monkeys in the acute stage of poliomyelitis. The monkeys treated with hypertonic salt solution intravenously and shortly after with convalescent serum intraspinally and intravenously showed improvement as compared with the controls. They suggested that there might be three reasons for this: use of larger amounts of serum than could otherwise be injected intraspinally; reduction of the edema of the cord; and a more intimate contact of the serum with the tissues of the central nervous system.

A single case with the ascending Landry type of paralysis was treated with convalescent serum intraspinally and 25 cc. of concentrated Ringer's solution (sodium chloride 18 per cent) intravenously. The patient recovered with residual paralysis.

Smith (1926, S 49) injected 40 cc. of a 30 per cent sodium chloride solution intravenously in a patient with progressing respiratory paralysis. This was followed by some reaction. The pulse became rapid and weak, and there was temporarily more respiratory embarrassment. Recovery ultimately followed, although some paralyses persisted.

The references to the use of hypertonic solutions are apparently meager. In a personal communication to the writer, Dr. Hubert S. Howe stated that he had used hypertonic glucose intravenously with resulting improvement in a large number of cases, both in the preparalytic stage and after the paralysis had developed. This treatment relieved signs of meningeal irritation and apparently checked the progress of paralysis in some instances, and accelerated the return of function.

In order to obtain good results freshly prepared solutions of pure glucose in adequate doses are necessary. Dr. Howe recommends 100 to 250 cc. of a 25 per cent solution, depending on weight of the patient, repeated every 12 to 24 hours. The hypertonic glucose is much to be preferred to a hypertonic salt solution. In addition to relieving the edema of the brain and cord and lowering the pressure of the spinal fluid, it adds nutrient fluid to the tissues and stimulates the action of the heart.

**Lumbar Puncture.** As the spinal fluid is usually under increased pressure in the early stages of poliomyelitis, the relief of this pressure by lumbar puncture is a rational procedure. It is reasonable to believe that it will also lessen the edema of the tissues of the central nervous system. Concetti in 1900 (C 23) commented briefly on the improvement in symptoms following the withdrawal of spinal fluid.

Müller (M 52) states that lumbar puncture has a favorable effect.

Römer (R 25) writes: "Lumbar puncture appears to me to be a rational method of treatment, because I have found increase of fluid sometimes in monkeys."

During the epidemic in New York City in 1916 lumbar puncture was used extensively for diagnosis, and to some extent for treatment, on account of the improvement that often followed the diagnostic puncture.

The following comments are taken from the Monograph on The Epidemic of Poliomyelitis in New York City in 1916. At the Kingston Avenue Hospital, it seemed that "improvement of paralysis was more rapid in cases in which lumbar puncture was performed. The relief of hydrocephalic symptoms following puncture was marked and often complete." At the Queensboro Hospital "the opinion of the visiting and resident staff was definite that in cases showing serious symptoms



better results were obtained from the use of simple puncture (single or multiple) than when puncture was followed by the use of any serum or medicament."

The physicians of the meningitis division of the Department of Health of New York City expressed their opinion that "the best results of treatment in early cases are obtained by complete rest, with lumbar puncture for the relief of signs of meningeal irritation" (N 3).

Le Boutillier (1917, L 21) recommended lumbar puncture both for diagnosis and as a therapeutic measure.

Schanz (1924, S 8) reports that he treats patients with poliomyelitis by repeated lumbar puncture, with, in his opinion, favorable results.

Wolff (1925, W 27) states that he treats all patients by lumbar puncture. In almost all, improvement was so prompt that he could ascribe it only to lumbar puncture. Müller (M 55) in 1925 again calls attention to the beneficial effects of lumbar puncture through its reduction of pressure in the rapidly progressing types of the disease, particularly when there are signs of meningeal irritation.

Montgomery and Cole (1925, M 43) reported a study of 26 cases of poliomyelitis, in 20 of which the diagnosis was made in the first week. In 16 cases in which lumbar puncture was done not later than the third day after the onset of meningeal symptoms, paralysis occurred in only 2 instances and consisted of a temporary slight weakness of the palate and a temporary ptosis of the lid. In 6 cases in which lumbar puncture was done later than the third day, paralysis developed in 5 instances. The remaining 4 cases were seen late and all were paralyzed.

The authors called attention to the marked improvement in symptoms which invariably followed the removal of the spinal fluid,—the cessation of vomiting, and the lessening of the hyperesthesia and the rigidity of the neck and spine.

The authors conclude: "The data that we have gathered strongly suggest a possible beneficial effect on the outcome of the disease to be derived from early and repeated subarachnoid drainage. We are making this report in the hope of stimulating further observations on a larger scale. The evidence of beneficial effect is sufficiently suggestive to necessitate the controlling of this factor in any studies of clinical poliomyelitis that attempt to evaluate a therapeutic procedure of which lumbar puncture is a part."

It is evident from these reports that in the early stages of poliomyelitis lumbar puncture is practically always followed by a marked improvement in symptoms. My own experience certainly corroborates

this. Certain observers also have the impression that the relief of the increased pressure of the fluid may be a factor in preventing the development of paralysis or in modifying its progress.

### Administration of Serum

The use of serum has attracted more attention than any other method of treatment for the acute stage of poliomyelitis.

In addition to convalescent serum and other sera possessing virucidal properties, normal horse serum has been used, as well as sera immune to various organisms, notably Rosenow's antipoliomyelitis streptococcic serum.

**Nonspecific Sera.** Normal horse serum was given intraspinally to some extent during the epidemic of 1916 in and around New York City. There were several favorable reports, but when the complete series was analyzed it was found that its use was not justified (N 20). In a few instances diphtheria antitoxin, antimeningitis serum, and other immune sera were used.

Ayer (1929, A 52) while reporting primarily on the use of convalescent serum, states that 23 cases received antipneumococcic serum only, and that 8 additional cases were given an initial dose of antipneumococcic serum and a subsequent dose of convalescent serum. The serum was given in all instances intraspinally. The results, Ayer says, were about the same with the antipneumococcic serum as with the convalescent serum, so far as could be judged by the smaller number of cases receiving the former. Ayer suggested that "the apparently beneficial results might be partially due to the phagocytic action of the additional aseptic meningitis produced by this introduction of a foreign serum." He also called attention to the various forms of serum sickness following the use of horse serum.

There seems to be no reason to comment on the use of nonspecific sera in poliomyelitis. That horse serum may give rise to dangerous reactions when injected intraspinally was amply demonstrated in New York City in the epidemic of 1931. Since this is so, the use of such sera intraspinally should be discontinued. There seems to be no justification for its use by any route.

Rosenow's antipoliomyelitis streptococcic serum has been used extensively. His reasons for believing that poliomyelitis is caused by a special strain of the streptococcus are presented in the *Section on Bacteriology* in the *Chapter on Etiology* together with details of the studies that have been carried out to prove and to disprove this theory.



Since 1917 Rosenow has published many papers on the preparation, properties, and therapeutic use of his serum. The experimental studies are described in the *Section on Bacteriology*. A similar serum, produced by Nuzum and Willy, is described in the same section. Rosenow and also Nuzum and Willy claimed that their sera had neutralizing properties against the virus of poliomyelitis. On the other hand, Amoss and Eberson (A 21; A 22) in 1928 stated that both Rosenow's serum and the serum of Nuzum and Willy not only failed to neutralize the virus but seemed even to promote the infection. Stewart and Haselbauer (S 56) in 1928 reported that Rosenow's serum, both concentrated and unconcentrated, failed to neutralize the virus. The same result was obtained by Morgan and Fairbrother (M 46) in 1930 with Rosenow's concentrated serum.

These failures of the serum, in the hands of experienced workers, to neutralize the virus indicate that it can have no specific effect. Yet the reports of its use have been distinctly favorable. Rosenow (R 47) in 1930 reviewed his previous publications, giving a complete bibliography, and reporting on the results of treatment of 158 new cases. He stated that in a series of 1113 cases, treated with Rosenow's serum, reported in 1927, the mortality rate and the incidence of residual paralyses were much lower than in control cases in which serum was not administered (R 51). The control cases "occurred at about the same time and under similar conditions, usually in the same locality and always in the same state" as the treated cases with which they were compared. While the results were most marked when the serum was given in the early stages of the disease, Rosenow states that it seemed to have curative power even when injected after marked paralysis had developed, as shown by the fact that the mortality rate in that group was less than half of that in the control cases. The case fatality of the 278 control cases was 29.5 per cent while of the 1113 treated cases it was 14.3 per cent, and of 269 cases with no paralysis at the time of treatment it was only 2.9 per cent. Of 177 control cases 31 per cent had no residual paralysis, as against 45.3 per cent of 866 treated cases. Whether paralysis was mild, moderate, or marked higher percentages of improvement occurred among the treated than among the untreated cases.

In Rosenow's new series of 158 cases, similarly favorable results are reported. The mortality rate was 10 per cent, as compared with a rate of 33 per cent in 39 control cases.

In Rosenow's earlier papers he advised that the serum be given intravenously. In his later papers he has recommended the intramuscular

route. He suggests 2 or more injections from 12 to 24 hours apart. Sometimes as many as 6 injections were made. The exact dose is not given. The average amount was 62 cc.

It is unnecessary to report the papers of other physicians—Rowan, Sugg, Clarke, and Dow and Diveley—to whom Rosenow refers and whose results are comparable to his.

The reason for these apparently good results is probably to be found in the inadequacy of the controls. This will be discussed in more detail later, in considering the effects of treatment by means of convalescent serum.

It may be noted that the Council on Pharmacy and Chemistry of the American Medical Association (A 11) when commercial firms submitted serum from horses immunized by streptococci from poliomyelitic patients, did not accept it.

**Sera with Neutralizing Power.** It has been demonstrated that various sera have the power of neutralizing the virus of poliomyelitis: the serum of persons who have had an attack of poliomyelitis, the serum of many individuals who give no history of the disease, the serum of monkeys in which poliomyelitis has been experimentally produced, and the serum of horses and other animals in which an active immunity has been developed.

The elaboration of the scientific basis for the use of immune serum is given in detail in the *Chapter on Resistance and Immunity*. In brief it may be stated that Flexner and Lewis (F 42) in 1910 discovered that monkeys surviving the experimental disease could not be reinfected; shortly after, in the same year, Römer and Joseph (R 28) demonstrated that the serum of monkeys surviving the experimental poliomyelitis had the power of neutralizing the virus *in vitro*. In the same year Flexner and Lewis (F 45) and Netter and Levaditi (N 8) proved that the same neutralizing power was to be found in the serum of individuals who had recovered from an attack of the disease. Flexner and Lewis (F 46) also showed that the intraspinal injection in monkeys of serum from monkeys or individuals recovered from poliomyelitis had the power of preventing paralysis or of prolonging the incubation period, if given within 24 hours after the inoculation of the virus.

These experiments formed an excellent basis for the use of convalescent serum in treating poliomyelitis.

**Convalescent Serum.** Netter was the first to make use of this method of treatment. His first case was treated in October, 1910, and a report of 4 cases was published in 1911 by Netter, Gendron and



Touraine (N 7). In all of the patients paralysis had already developed when the treatment was begun. The convalescent serum was injected intraspinally in amounts of 3 to 15 cc. The injections were repeated—1 patient receiving 9 and the others 3 doses. One patient died. The other 3 showed prompt improvement. The results were compared with those of 19 other patients, 6 of whom received intraspinal injection of antimeningococcic serum. The authors were encouraged by the results of the convalescent serum treatment.

In 1915 Netter (N 5) published the result of the use of convalescent serum intraspinally in 32 patients, including the 4 reported in 1911. In only 1 instance was the serum given in the preparalytic stage and this patient recovered rapidly after 2 injections without the development of paralysis.

Netter used 5 to 13 cc. of serum. In some instances only 1 injection was given, in others as many as 10. It was noted that a meningeal reaction usually followed the injection of the serum and in 2 instances this was quite severe.

Eight of the 32 patients died. In 6 the cure was stated to be rapid and complete, and in 3 others recovery was nearly complete. In 7 instances there was marked improvement; in 5, appreciable improvement, for which the effect of the serum might be questioned; and in 3 there was no change.

Netter believed that the effect of the serum when administered in 3 stages of the disease should be considered; in the preparalytic stage, it might prevent the development of paralysis; while the paralysis was progressing, it had the power to check its advance and to cause the paralysis already developed to disappear; after the paralysis had reached its maximum, it aided in reparation.

In a later communication Netter (1928, N 6) stated that the intramuscular route was to be preferred to intraspinal or intravenous injections.

During the epidemic of 1916, convalescent serum was very extensively used. The results obtained seemed, for the most part, favorable. Since that time proponents of the value of convalescent serum have appeared in all localities in which poliomyelitis has been prevalent.

Certain physicians have maintained, because of the lack of adequate controls, and because they have observed favorable results in many cases where serum has not been given, that the value of the serum has not been proved. But their objections have been given little consideration.

It does not seem necessary to review all the references to the use of convalescent serum. An effort has been made to select reports of large numbers of cases, of different methods of administering the serum, and of epidemics in different localities.

In the earlier reports the serum was given only intraspinally, in an amount somewhat less than the spinal fluid withdrawn, as a rule 10 to 15 cc., and the injection was usually repeated 2 or 3 times.

Zingher (Z 5) treated 54 patients in the preparalytic stage, of whom 44 did not develop paralysis and none died. Of 119 cases treated after the development of paralysis, 45 resulted fatally. Zingher also used normal human serum in 10 patients in the preparalytic stage, 9 of whom recovered without paralysis and 1 died; 5 deaths resulted in 33 paralyzed patients, similarly treated.

While Zingher did not draw definite conclusions from his group of cases, he expressed the opinion that the action of the convalescent serum was beneficial, especially in the preparalytic stage.

Draper (1917, D 19, D 18) reported 46 cases treated with convalescent serum in the preparalytic stage, injected intraspinally in most instances. In 20, or 43.5 per cent, no paralysis occurred; in 26 paralysis developed and 7 died. Of 33 cases receiving no serum, the final result of 3 is not given; of the remaining 30, 19 or 63.3 per cent did not develop paralysis, but 11 became so with 3 deaths. Draper states that while the data from his series of cases are inconclusive, the clinical impressions and observations favor the use of convalescent serum. He believes that the serum is of benefit especially in the first 30 hours after the onset of meningeal symptoms. He thinks that the question of the value of serum after the development of paralysis has not been definitely settled. He recommends that the serum be given by the intraspinal combined with the intravenous or subcutaneous routes.

Peabody (P 6) treated 51 cases in the preparalytic stage and 60 recently paralyzed cases, using about 10 cc. of serum intraspinally and giving from 1 to 4 treatments at intervals of from 12 to 24 hours. Of the 51 preparalytic cases, 35, or 69 per cent, recovered without paralysis; 11, or 21 per cent, recovered with paralysis; and 5, or 10 per cent, died. The results in the patients already paralyzed were not significant. The case fatality—32 per cent—was somewhat higher than the average for the epidemic, which is given as 21 per cent. Peabody's conclusions are conservative. He states: "For the proper interpretation of the results of treatment it is essential that we should have a much more complete knowledge of the natural history of the disease. At the present time



we have only an imperfect idea as to what proportion of persons affected with the disease become paralyzed even if no treatment is instituted. Nevertheless there is apparently a general agreement among those who have used immune serum as to its harmlessness, and as to the fact that in certain, possibly numerous instances its administration is beneficial."

Amoss and Chesney (A 20) were, so far as I know, the first to administer convalescent serum by both the intraspinal and intravenous routes. They employed the intravenous route for several reasons. A larger quantity of serum could be administered in this way, the serum might flow directly to the interstices of the nervous tissues, and the rapidity of outflow of the serum in the subarachnoid space might be diminished. From 5 to 20 cc. of serum were given intraspinally and from 20 to 100 cc. intravenously, or in some instances subcutaneously. The injections were not repeated.

In 12 cases in which there was paralysis at the time serum was first given, 1 patient died; in 2 there was some extension of the paralysis; and in 9 the paralysis did not progress.

In 14 cases there was no paralysis when the serum was administered. Two of these patients died of respiratory paralysis, 2 others developed some degree of paralysis, and 10 (71 per cent) showed no paralysis.

The authors note that after the administration of serum the temperature tended to fall rapidly to normal, and suggest that the temperature curve may indicate whether or not additional injections of serum are needed. They state: "It seems highly desirable, therefore, to administer at least 50 cc. of serum in every case, and if possible to treat cases within 30 hours after the onset of the first symptoms."

Schwarz (1916, S 25) treated 21 cases in the preparalytic stage with convalescent serum intraspinally. The injections were usually repeated 2 or 3 times. Of these, 9 did not develop paralysis. Of 21 patients who did not receive serum, 17 escaped without paralysis. Schwarz did not observe any clinical improvement following the injection of the serum, and he noted that the untreated group had a larger percentage of non-paralytic cases. However, he did not consider that the series was large enough to furnish conclusive evidence in regard to the value of the serum.

The consensus of opinion after the epidemic in 1916 was that the serum was not of value after the development of paralysis. Ulrich (U 1) for example, reporting on a series of 114 cases, divided into 5 groups, treated after the development of paralysis by (1) immune serum intraspinally, (2) normal human serum intraspinally, (3) auto-

therapy (intramuscular injection of patient's own spinal fluid), (4) repeated lumbar puncture, and (5) untreated, found essentially the same result in all 5 groups.

As time went on there was a divergence of opinion in regard to the best method of administering the serum. In the early part of the 1916 epidemic the serum was given only intraspinally. In the latter part of the epidemic, as has been stated, Amoss and Chesney, and Draper advised the simultaneous injection of serum intravenously, subcutaneously or intramuscularly. This method was generally followed in the succeeding years in the eastern part of the United States and in Australia. In California and in Canada, intramuscular injections were generally used. Shaw, Thelander, and Fleischner (1925, S 37) advocated this method because it is simple and safe and because poliomyelitis is understood to be a general infection in its early stage. Shaw and Thelander published a second report in 1928 (S 35) and a third in 1930 (S 36) summarizing the cases treated from 1920 to 1930. They gave the serum in doses of from 30 to 100 cc. and repeated the injections at 12-hour intervals, sometimes giving as many as 4 doses. They describe 112 cases, of which 23 were treated in the preparalytic stage. None of these developed permanent paralysis but almost one-third showed temporary weakness. In 33 instances treatment was begun in the early stage of paralysis while there was fever. The authors did not consider that it was possible to judge results at this stage, but they did recommend that patients showing bulbar symptoms should be treated intensively during the febrile period.

In 1928 an epidemic of poliomyelitis occurred in Manitoba. In this outbreak serum was given intramuscularly in doses of 25 cc. In some instances the injection was repeated.

McEachern, Chown, Bell and McKenzie (1929, M 3) reported on 161 cases, dividing the series into 4 groups:

- (1) 57 cases which received 1 dose (average 25 cc.) of serum intramuscularly in the preparalytic stage; 53 recovered completely, and 4 showed residual paralysis.
- (2) 17 cases which received 2 or more doses of serum intramuscularly in the preparalytic stage; 16 made a complete recovery; paralysis persisted in one.
- (3) 33 cases which received serum after onset of paralysis; only 7 recovered without paralysis; 15 showed residual paralysis.
- (4) 54 cases which received no serum; 14 recovered and 34 were paralyzed.



The authors conclude:

1. Convalescent serum is of value when administered in the preparalytic stage.
2. The intramuscular route is simple, safe and sufficiently efficacious to justify its use during an epidemic.

Similar conclusions were reached by McKenzie (1929, M 7) in a later analysis of these same cases and of 158 additional cases in regard to which complete data were not available.

Lomer and Shirreff (1930, L 63) reported on the use of convalescent serum intramuscularly, usually 25 cc., in an epidemic in Ottawa, Ontario, in 1929. Of 115 cases treated in the preparalytic stage, 109 (94.8 per cent) recovered without paralysis; 5 (4.3 per cent) recovered with paralysis; and 1 (0.9 per cent) died without paralysis. It is stated that 1 of the cases developing paralysis received only 10 cc. of serum. The serum was also given to all cases in which paralysis had not been established for more than 2 days. The authors state that the serum apparently had little or no effect after the onset of paralysis.

McKay and Hardman (1931, M 5) published data of a second outbreak in Ontario in 1930, in which convalescent serum was used in doses usually of 20 cc. The route of administration is not given, but it may doubtless be assumed that intramuscular injection was again used. In this epidemic 414 cases were treated before paresis or paralysis had developed. The cases were divided into groups, depending on the day of illness on which the serum was given. All the patients (185) treated on the first day recovered without paralysis. Of 125 treated on the second day, 94.4 per cent had no paralysis. The percentage of recovery without paralysis dropped as time went on—71.6 per cent of those treated on the third day; 62.1 per cent of those treated on the fourth. Relatively few were treated after the fourth day. It was thought, apparently, that some improvement followed the use of serum after there was paresis, but little or any after real paralysis.

Reference is made to the lack of controls, and it is stated: "To withhold serum treatment for this purpose would be unwarranted in such a disease as poliomyelitis with its far-reaching and permanent disabilities."

The authors conclude that the experience of 2 years with convalescent serum in Ontario shows it to be of considerable value and recommend that its use be continued.

Ayer (1929, A 52) reported a series of 126 cases diagnosed and treated in the preparalytic stage. These cases occurred in and near Syracuse,

New York. Ayer used convalescent serum intraspinally in all except a few cases (31) in which either antipneumococcic serum only was given, or (in 8 of these cases) antipneumococcic serum followed by convalescent serum. The injection of the serum was repeated if at the end of 18 to 20 hours the temperature was 101°F. or higher. It has already been stated that the results in the patients receiving the nonspecific serum were essentially the same as in those receiving convalescent serum.

Of the 126 cases, 8 died, 25 developed paralysis, and 93 were reported as recovering without paralysis, although it is stated that in a few of these a later examination showed some insignificant weakness.

Ayer was convinced of the specific value of the convalescent serum in spite of the results with the nonspecific serum, and also of the possible value of lumbar puncture.

Aycock and Luther (1928, A 48) treated 106 patients in the preparalytic stage of poliomyelitis in 1927. The patients were given 2 intraspinal injections of convalescent serum at 24-hour intervals and 1 dose intravenously when first seen. Of these patients only 1 died, a mortality of 0.9 per cent compared with a mortality rate of 14 per cent for Massachusetts in 1927. Of the remaining treated cases 64 per cent developed paralysis. It is stated, however, that the degree of paralysis was much less in the treated cases than in those cases that received no serum. The measurements of the paralyses were made about 2 months after the onset of the disease. A comparison of the outcome was made between the results in the 106 treated cases with others untreated in the same year; the untreated patients represented all those seen and examined in the after-care clinics of the Harvard Infantile Paralysis Commission.

|                                                                                    | <i>Treated</i> | <i>Untreated</i> |
|------------------------------------------------------------------------------------|----------------|------------------|
| Percentage of mortality.....                                                       | 0.92           | 14.0             |
| Percentage with no paralysis.....                                                  | 33.0           | 1.2              |
| Average total paralysis.....                                                       | 19.0           | 65.6             |
| Percentage of cases in which paralysis of the two<br>severer grades developed..... | 5.7            | 46.0             |

The writers state that the figures for the untreated cases were, to some extent, selected, since many with a mild and a nonparalytic condition probably did not visit the clinics.

In a later article, Aycock, Luther, and their associates (A 51) reported on 116 additional cases which occurred in Massachusetts in 1928 and were treated in the preparalytic stage. The same method of treatment was used, but as there was a larger supply of serum, the average dose was larger, 102 cc. in 1928 as compared with 54.8 cc. in



1927. The case fatality rate was 6.4 per cent, while for the untreated cases it was 17.8 per cent. Of the treated cases, paralysis developed in 61.2 per cent, but the degree of paralysis was less by measurement than that of the untreated cases.

Since 1925 Dr. Jean Macnamara has been working intensively on poliomyelitis in Australia. A number of papers on this work have been published, and the results of the treatment with convalescent serum from 1925 to 1931 are summarized by Macnamara and Morgan in 1932 (M 12). The authors have chosen the term poliomyelo-encephalitis in preference to poliomyelitis. They collect and handle their serum with strictly aseptic precautions, and by the methods used obtain a serum, free from hemolysis and fibrinogen, to which no anti-septic is added. The use of this serum, they state, is not followed, when injected intravenously or intraspinally, by such reactions as are mentioned by most other workers.

As in other places in which serum has been used, an effort was made to educate the physicians and the public in the early symptoms of poliomyelitis. It is stated that in 1925 only 1 case was diagnosed in the stage before paralysis, while in 1931, 86 out of 270 cases were treated in the preparalytic stage.

The initial dose of serum in preparalytic cases was usually 50 cc. or more, injected intraspinally and intravenously. If the temperature did not fall within 18 hours and the general condition of the patient was not greatly improved, a second dose of 30 to 40 cc. of serum was given intravenously. The authors state: "In our series, if the patient had not improved within 20 hours, there has been one reason only—insufficient dosage". If a patient was seen within 24 hours after the onset of paralysis and there was still fever, 40 to 60 cc. of serum was given intravenously. "The usual but not invariable sequence has been an immediate fall of temperature and an arrest of the paralysis at the stage existing when the injection was made." Serum was not given to paralyzed patients with normal temperature.

In the years 1925 to 1931, 133 cases were diagnosed and treated before paralysis appeared. Of these cases only 1 died, and 6 developed extensive paralysis. The results in the fatal case and in 5 of the badly paralyzed cases are explained by a period of delay between the withdrawal of a large quantity of spinal fluid and the administration of serum. In the seventh case only 1 injection of serum was given, 30 cc. intramuscularly—a dose considered to be inadequate. The authors consider that the withdrawal of a large amount of spinal fluid may be

harmful. In 60 of the total cases paresis developed which cleared up rapidly and completely, leaving 66 cases in which no paralysis developed at any time.

Macnamara and Morgan, therefore, recommended the use of human immune serum in preparalytic cases, and in febrile patients within 24 hours after the development of paralysis. "If given later, when paralysis is stationary, serum is of no value." The treated cases were compared with the untreated cases using the standards of the Harvard Infantile Paralysis Commission for measuring the degree of paralysis. In the epidemic of 1930-1931, of 76 treated cases only 5.2 per cent were affected by more severe grades of paralysis, while of 151 untreated cases the percentage was 58.2. The authors state: "It is admitted that the only accurate method to assess the results of any therapy in preparalytic poliomyelitis would be the treatment of alternate cases, leaving the remainder as controls. In Australia this could not be done."

In neither the Rumanian epidemics of 1927-1928, nor in the Alsatian epidemic of 1930 was convalescent serum used on a sufficiently large scale to give adequate data.

**Immune Horse Serum.** The reports on the use of convalescent serum, which were quite consistently favorable, led to a large demand for this serum. On account of the obvious difficulties in procuring it in large quantities, efforts were made to immunize horses in the hope of developing a source for an adequate supply of an immune serum. The account of these experiments is given in detail in the *Chapter on Resistance and Immunity*. It is sufficient here merely to relate that Neustaedter and Banzhaf (N 14) in 1917 produced a horse serum which gave some evidence of ability to neutralize virus in a few experiments and which was used therapeutically in a limited number of cases. In 1917 Pettit (P 14) began the production of a horse serum which was more extensively used. His experiments have continued up to the present time. While some doubt was expressed in the past in regard to the possibility of producing a virucidal serum in a horse, Pettit stated in a personal communication to me that he had proved that his serum did have the power of neutralizing the virus. Weyer, Park, and Banzhaf (W 17) in New York, and Fairbrother (F 4) and Fairbrother and Morgan (F 7; F 8) in London, were successful in immunizing horses and producing a serum the virucidal potency of which was comparable to that of human convalescent serum. Weyer, Park and Banzhaf (W 17), moreover, increased the potency of the serum



about 4-fold by concentration. Schultz and Gebhardt (S 15) in California also succeeded in immunizing a horse.

Pettit's horse serum has been used clinically more extensively than any other horse serum. And even this has been administered in comparatively few instances in the preparalytic stage. Etienne of Nancy (E 19) reported on the results in 13 cases, treated adequately by the serum. The exact stage of the disease is not stated. Of these cases 11 recovered completely, 1 recovered with slight residuals, and 1 died. Etienne recommends large doses of serum, 80 to 100 cc., repeated until a total dosage of 600 cc. or more has been given. In mild cases he prefers intramuscular injection, in more severe types a combination of intraspinal with intravenous or intramuscular injection.

Marinesco, Manicatide, and State-Draganesco (M 19) used Pettit's serum in 30 cases at the period when paralysis was beginning. Of these patients 6 died; in 7 there was a slight degree of paralysis; in 8, moderate; and in 9, severe.

Rohmer, Meyer, and their associates (R 33) report that 83 children were treated at the beginning of the disease with Pettit's serum. In certain instances the dose was considered insufficient, but the authors concluded that the results gave no proof of the therapeutic value of the serum.

The refined and concentrated horse serum prepared by Park, Weyer and Banzhaf was used in a fairly large series of cases in 1931. At first this was given intraspinally but on account of the severe and sometimes fatal reaction that followed, this method was soon discontinued. Thereafter it was usually given intramuscularly and in a few cases, intravenously, in a dose averaging 20 cc. The results in a series of 63 cases are tabulated. This is not a complete list of all the cases treated by this serum, but it may be accepted as being representative. The results given here are taken at the end of 4 to 7 months.

|                   | <i>Number</i> | <i>Per cent</i> |
|-------------------|---------------|-----------------|
| Total.....        | 63            |                 |
| No paralysis..... | 44            | 69.8            |
| Weakness.....     | 2             | 3.2             |
| Paralysis.....    | 10            | 15.9            |
| Deaths.....       | 7             | 11.1            |

Except for the higher case fatality which was undoubtedly due to the reactions following the intraspinal administration of the serum, the results are about the same as those obtained by the use of the convalescent serum at the same time.

**Immune Sheep, Goat, and Monkey Serum.** Other animals, such as sheep, goats, and monkeys, have also been used to produce an immune serum. Pettit produced a sheep serum shortly before he immunized the horse. In 1929 he (P 16) reported on the immunization of the monkey. He referred to the use of the monkey serum in only 1 case, in which treatment was begun on the eleventh day. Some improvement was reported. In 1932 Pettit, Erber and Kolochine (P 18) published an account of the results obtained in immunizing a chimpanzee. The advantages of the use of this animal are summarized as follows: the chimpanzee gives a larger amount of serum; the elaboration of immune bodies proceeds more rapidly and reaches a high titer; the serum of anthropoids is tolerated perfectly by the human organism.

Howitt and others (1931, H 37) immunized both sheep and goats and used the serum in the treatment of 12 patients in the preparalytic stage. Of these, 8 developed no paralysis, and 4 a transient weakness. The injections were given intramuscularly usually in doses of 50 to 100 cc.

**Discussion.** A study of the reports of the use of immune serum in general, and especially of the convalescent serum which has been tried in by far the largest series of cases, reveals certain points of interest. In most instances the only controls have been cases with paralysis, occurring in the same neighborhood at about the same time. The only 2 exceptions to this has been the reports of Schwarz and Draper, already summarized, in which untreated cases observed in the preparalytic stage resulted more favorably than the cases receiving convalescent serum.

In most of the articles it is either expressed or implied, that in the various localities very few cases of poliomyelitis were diagnosed in the preparalytic stage prior to the advent of the use of convalescent serum. With the hope of a successful method of treatment, the keenest interest of the medical profession and of the public was aroused in the diagnosis of the disease in the earliest stage possible. This resulted, it is reasonable to assume, in the reporting of large numbers of cases which otherwise would have remained unrecognized. For it has been known since the time of Caverly that nonparalytic cases occur, yet there are few references to untreated nonparalytic cases.

Again, although different groups of workers insist that the serum, to be effective, must be used in a certain way—intraspinally, intraspinally and intravenously or intramuscularly, or intramuscularly—a study of the reports shows that the results by all methods were essen-



tially the same. And most striking of all, the reports of Rosenow's serum showed even better results than those of convalescent serum.

For all these reasons, certain physicians have remained skeptical of the value of immune serum. Duhem (1931, D 29) quotes Nobécourt, who, after having studied at length a number of patients who had received serum treatment, expressed his conclusion in these words: "There does not seem to be at the present time any truly specific treatment for the acute stage of poliomyelitis. . . . The serum of recovered patients, Pettit's serum, and autohemotherapy, must, it seems to me, all be placed on the same plane."

Morse (1929, M 48), while apparently unconvinced of the value of convalescent serum, expressed the opinion that its use should be continued, but advised that it be employed with an open mind. Crothers (1926, C 33) referring to use of convalescent serum, wrote: "My impression is strong that no really conclusive proof of its value exists."

In 1917, Neal, Abramson, and associates (N 3) expressed their disbelief in the value of the convalescent serum, being influenced by their observations of treated cases, and of a fairly large number of cases (202) seen by them in the preparalytic stage. Practically all of these received no serum, and yet at the end of 2 months 173 had recovered without paralysis, while in 29 a mild degree of paralysis persisted. Records were not kept in regard to the development of an earlier paralysis which may have disappeared in the interval. They even suggested that in certain instances the intraspinal injection of serum might be harmful on account of the aseptic meningitis that usually develops.

#### RESULTS OF TREATMENT WITH CONVALESCENT SERUM COMPARED WITH THE RESULTS IN UNTREATED CONTROLS IN THE 1931 EPIDEMIC

At the beginning of the epidemic of poliomyelitis in and around New York City in the summer of 1931, there was this divergence of opinion in regard to the value of convalescent serum, with the weight of opinion in its favor. Park therefore suggested that an effort be made during this epidemic to compare the results in a large series of cases receiving the convalescent serum in the preparalytic stage with an approximately equal number of cases diagnosed in the preparalytic stage but receiving no serum. These studies were made by clinicians of the Health Department and the Hospitals for Contagious Diseases, and by the clinicians working under the direction of the poliomyelitis section of the Public

Health Relations Committee of the New York Academy of Medicine. Another study with control cases was carried out by Kramer, Aycock, and associates (K 25) at two hospitals, one in Brooklyn, New York, and one in Hartford, Connecticut. In these hospitals 82 cases were diagnosed in the preparalytic stage, approximately half of which received convalescent serum by the intravenous and intraspinal routes, while the other group received no serum. The authors state: "Of the eighty-two cases of poliomyelitis which were studied in Brooklyn and Hartford, forty-two, or 51 per cent, developed some paralysis, this number being

TABLE 9

TREATMENT OF PREPARALYTIC CASES WITH CONVALESCENT SERUM, NEW YORK CITY, 1931; RESULTS AT THE END OF 3 WEEKS\*

|                                      | TOTAL CASES | NO WEAKNESS<br>OR PARALYSIS AT<br>END OF 3 WEEKS |          | WEAK-<br>NESS |          | PARALYSIS |          | DIED   |          |
|--------------------------------------|-------------|--------------------------------------------------|----------|---------------|----------|-----------|----------|--------|----------|
|                                      |             | Number                                           | Per cent | Number        | Per cent | Number    | Per cent | Number | Per cent |
| <i>Controls:</i>                     |             |                                                  |          |               |          |           |          |        |          |
| Observed by Health Department.....   | 306         | 229                                              | 74.8     | 46            | 15.0     | 29        | 9.4      | 2      | 0.7      |
| Observed by Academy of Medicine..... | 102         | 72                                               | 70.5     | 12            | 11.7     | 16        | 15.6     | 2      | 2.0      |
| Combined totals.....                 | 408         | 301                                              | 73.7     | 58            | 14.2     | 45        | 11.0     | 4      | 0.9      |
| <i>Convalescent serum:</i>           |             |                                                  |          |               |          |           |          |        |          |
| Observed by Health Department.....   | 95          | 72                                               | 75.7     | 10            | 10.5     | 10        | 10.5     | 3      | 3.8      |
| Observed by Academy of Medicine..... | 424         | 285                                              | 67.2     | 30            | 7.0      | 92        | 21.7     | 17     | 4.0      |
| Combined totals.....                 | 519         | 357                                              | 68.8     | 40            | 7.7      | 102       | 19.6     | 20     | 3.8      |

\* Figures taken from a paper read by Dr. William H. Park before the American Medical Association, New Orleans, May, 1932.

about equally divided between the two cities. There were two deaths from respiratory paralysis. Both of these were in the treated group, one in Brooklyn and one in Hartford. In the remaining cases the average paralysis for the treated group in Brooklyn and Hartford combined was 12.1 and for the untreated group, 5.9 . . . this difference between treated and untreated cases is due to a relatively few severely paralyzed cases in the treated series which are sufficient to affect markedly the average for the whole group."



Tables 9 and 10 show the comparison between treated and untreated cases diagnosed in the preparalytic stage by the physicians of the Health Department and of the Committee of the Academy of Medicine. The treated cases received the convalescent serum in rather large doses (40 to 100 cc.) and by various combinations of routes, usually intraspinally and intravenously or intraspinally and intramuscularly. No decisive evidence in favor of any method of administration was secured. These data are taken from a paper read by Park before the American Medical Association in New Orleans, May, 1932.

TABLE 10  
TREATMENT OF PREPARALYTIC CASES WITH CONVALESCENT SERUM, NEW YORK CITY, 1931; RESULTS AT THE END OF 4 TO 6 MONTHS\*

|                                      | TOTAL<br>CASES | COM-<br>PLETE<br>RECOV-<br>ERY | WEAK-<br>NESS | PARALY-<br>SIS | DIED |
|--------------------------------------|----------------|--------------------------------|---------------|----------------|------|
| <i>Controls:</i>                     |                |                                |               |                |      |
| Observed by Health Department.....   | 306            | 243                            | 22            | 38             | 3    |
| Observed by Academy of Medicine..... | 100            | 83                             | 8             | 7              | 2    |
| Combined totals {                    | 406            | 326                            | 30            | 45             | 5    |
|                                      |                | 80.3                           | 7.3           | 11.1           | 1.2  |
| <i>Convalescent serum:</i>           |                |                                |               |                |      |
| Observed by Health Department.....   | 99             | 83                             | 11            | 2              | 3    |
| Observed by Academy of Medicine..... | 404            | 302                            | 34            | 51             | 17   |
| Combined totals {                    | 503            | 385                            | 45            | 53             | 20   |
|                                      |                | 76.5                           | 8.9           | 10.5           | 4.0  |

\* Figures taken from a paper read by Dr. William H. Park before the American Medical Association, New Orleans, May, 1932.

Conclusions

A group of more than 1000 cases, including those of Kramer and Aycock, diagnosed in the preparalytic stage, with approximately half treated by convalescent serum, shows nothing to indicate the therapeutic value of the serum, either in reducing case fatality or in preventing paralysis. Indeed, the slight differences between the treated and the untreated groups are against the use of serum. Since the same results were shown by three groups of workers—the physicians of the Health Department and Hospitals, the physicians working under the direction of the Subcommittee on Poliomyelitis of the Public Health Relations Committee of the New York Academy of Medicine, and

Kramer, Aycock, and their associates—it may be concluded that these cases were diagnosed and treated without personal bias. It is fair to say, however, that there is a belief that the percentage of moderately severe cases was a little greater in the treated children in the group studied under the direction of the Academy of Medicine. This number of cases seems large enough to equalize in each group the individual differences that cannot be exactly measured in clinical medicine.

The case for or against the use of convalescent serum may now be turned over to the judgment of the medical profession. It is hoped that if the treatment of the cases with convalescent serum is carried on by some that a careful record will be kept of the outcome of the cases and a similar study be made of an equal number of untreated cases.

#### TREATMENT OF THE PARALYSIS OF POLIOMYELITIS

**Treatment of Respiratory Paralysis.** It has already been stated that death in poliomyelitis is almost always caused by respiratory paralysis. At times this paralysis may be partial and recovery may take place without recourse to artificial means of maintaining respiration. In other instances a degree of respiratory paralysis incompatible with life may be temporary, and if breathing can be maintained by mechanical devices for a time, return of function takes place.

Durand (1929, D 31) believes that death may be due, in some instances, to “drowning” in the secretion of mucus which the patient can neither swallow nor raise. He therefore suggests a postural treatment which he has used with success. The patient is turned on his chest and his head is lowered so that the mucus drains through the mouth and nose.

Various methods of artificial respiration have been tried. The manual method is not adapted to prolonged use and the pulmotor has many disadvantages when applied to patients who are conscious.

The most suitable type of respirator is the Drinker. This is described by Drinker and McKhann (1929, D 20), and is now familiar to most physicians. It has been used more and more extensively in respiratory paralysis in poliomyelitis during the past 3 years, but there are few reports on the final results in any considerable number of patients.

Shambaugh, Harrison, and Farrell (1930, S 30) reported on 3 cases. One patient recovered after being in the respirator for 4 weeks constantly and for 2 hours a day for 6 weeks. The other 2 patients died, and at autopsy both showed broncho-pneumonia of the dependent



portions of the lungs. The authors concluded that pneumonia was the chief cause of death when life was prolonged by artificial respiration. They recommended putting the patient in the respirator early and keeping the lungs clear by frequent turning and periods of hyper-ventilation.

Shaw, Thelander, and Limper (1931, S 38) used the Drinker respirator in 15 cases. In 9 there was intercostal paralysis. All of these responded with symptomatic relief and 6 recovered. In 1 there was a diaphragmatic paralysis. The patient was kept comfortable for 7 weeks and the function was slowly returning.

In 5 patients there was bulbar paralysis and respiratory failure. While subjective relief was obtained death ensued in all these patients.

The authors conclude that the machine is chiefly of value in intercostal paralysis but that in all cases symptomatic relief is afforded. It is also of value in increasing respiratory excursions during convalescence.

Brahdy and Lenarsky, in an article about to be published, "Artificial Respiration for Respiratory Paralysis in Epidemic Poliomyelitis," summarize the results as follows:

"The cases treated in the respirator were divided as follows:

|                                                             | <i>Num-<br/>ber</i> | <i>Deaths after<br/>Discharge</i> |
|-------------------------------------------------------------|---------------------|-----------------------------------|
| Spinal cases discharged alive from Willard Parker Hospital. | 18                  | 6                                 |
| Spinal cases died at Willard Parker Hospital.....           | 16                  |                                   |
| Bulbar cases died.....                                      | <u>12</u>           |                                   |
| Total treated.....                                          | 46                  |                                   |

After the first few weeks bulbar cases were not considered suitable for treatment.

"Following discharge from Willard Parker Hospital deaths occurred after 14, 24, 24, and 45 days. The last three were having an uneventful convalescence and developed acute respiratory symptoms which may have been due to massive atelectasis—one autopsy failed to reveal pneumonia. Two other children died 5 and 8 months after discharge. One at home, from what was diagnosed as pneumonia, the other at Willard Parker Hospital from pneumonia (autopsy). The second child was admitted to the hospital about 6 weeks before death with scarlet fever and later developed varicella. Five weeks after admission and after the temperature had been normal several days she developed a pneumonia which was fatal in 9 days."

**Treatment of Paralysis in the Early Stage.** The scope of this book from a clinical standpoint is limited almost entirely to a consideration

of the acute stage of poliomyelitis. Therefore no attempt will be made to discuss in detail the best methods of dealing with paralyses and none whatever to describe the operative procedures that are carried out to correct deformity, and to secure restoration of stability and function. This important work lies in the domain of orthopedics, and there are comprehensive articles and books on the subject that may be consulted. Among these may be mentioned "Orthopedic Surgery," Jones and Lovett, 1929 (J 12); "A Treatise on Orthopedic Surgery," Royal Whitman, Philadelphia, 1930 (W 19); "Die Epidemische Kinderlähmung," Fritz Lange, Munich, 1930 (L 13); "Poliomyelitis," W. Russell MacAusland, Philadelphia, 1927 (M 1).

The early care of paralyzed muscles is so extremely important that a few general principles are given. Not a little of the unfortunate disability arising from the paralyses of poliomyelitis has been due to a lack of appreciation of what constitutes proper care in the early stage. Weakened muscles have been allowed to stretch and opposing muscles to contract, with resulting deformities. Physiotherapy and exercise have been begun before the acute stage has subsided, thereby seriously interfering with the natural tendency toward recovery which is usually shown.

The following brief outline of the early treatment of paralyses has been given in a personal interview by Charlton Wallace, to whose sympathetic and skilful treatment many sufferers from poliomyelitis during the past 25 years owe their partial or complete recovery from the disability resulting from the disease.

As soon as paralysis appears there must be complete rest and immobilization of the muscles and joints involved. In this way pain is lessened, and the overstretching of paralyzed muscles and contracture of opposing muscles, the chief cause of deformity, is prevented. The period during which rest and immobilization are indicated usually lasts about 3 weeks.

For paralyses involving the feet and legs, a plaster bandage should be applied, extending from the toes to just below the knees and maintaining the foot at right angle to the leg. The weight of these bandages should hold the knee and hip in proper alignment. It is but rarely necessary to use a long plaster spica.

When the back muscles are involved, a fracture board should be placed under the mattress to prevent sagging. The position of the patient should be maintained so that a deviation of the spinal column is avoided. In this type of paralysis, the patient should be kept in bed for a period of 3 months.



In paralysis of the upper extremities, abduction of the arm to at least a right angle with the trunk may be maintained by an aeroplane splint, extending along the forearm and under the hand; or the arms may be tied to the sides of the bed.

As soon as the acute stage has passed according to the indication in each individual patient, physiological use of the muscles should be begun. Patients with paralysis of muscles of the arm group may be up and about using aeroplane splints. Patients with paralysis of the legs, if the back muscles are not involved, may try walking with proper braces. Over-exercise or fatigue is absolutely contraindicated.

During the convalescent period, which is estimated to be usually from  $1\frac{1}{2}$  to 2 years, no treatment is a specific. Use is made of any form of physiotherapy which may be conducive to improvement—heat, massage, the sinusoidal current applied directly to the paralyzed muscles. Diathermy is the only method by which heat can be applied to deep tissues. The galvanic and faradic currents should be avoided. Muscle training should be used for all paralyzed muscles except those of the spinal group. In this region the paralysis is usually unilateral, and muscle training will over-develop the unimpaired muscles, thus producing an early rotary lateral curvature.

Exercise in water is of great value. Muscles in which no movement can be demonstrated when the patient is lying on the table, will manifest power when he is in the swimming pool.

It is desirable that treatment should when possible be given daily under the direct care of a properly trained physiotherapist. If the best results are to be obtained, the patient must follow implicitly the advice of a competent orthopedist.

## CHAPTER VI

### PATHOLOGY

#### DEVELOPMENT OF THE PATHOLOGICAL PICTURE

Heine (1840, H 18) was not only the first to give a scientific description of the clinical manifestations of poliomyelitis, but he was also the first to formulate a hypothesis concerning the pathological anatomy, although he was unable to support his theory with a single autopsy of his own. The only post-mortem finding on which he based his assumption was one on a case seen by Hutin (H 46) in the Hôpital Bicêtre in Paris in 1825. The case seemed to Heine analogous to his own cases and he assumed that the pathology would also be similar and that examination would show, to a greater or less degree, an atrophic condition of the cord. He pictured the disease process as an affection of the cord of an irritative and congestive character. The congestion produced an active exudate, which caused the sudden paralysis. The transitory nature of certain of these paralyses was explained by the assumption that the fluid exudate was re-absorbed in some portions but persisted in others, especially in the lower part of the spinal canal, and thus produced a permanent paralysis which more often involved the lower extremities. Difficulty, however, was found in reconciling his hypothesis with the fact that the anterior nerves seemed to be more severely injured than the posterior, but he thought that perhaps the anterior columns were affected by a more solid lymphatic exudate while the posterior were soon relieved by resorption of a more fluid exudate. In the second edition of his work in 1860, although he had no fresh grounds for his belief, Heine was so convinced of the correctness of his idea of the spinal origin of the disease that he used the title "*Spinale Kinderlähmung*" and urged, in opposition to certain other workers, that the disease receive the name *Paralysis infantilis spinalis*.

Rilliet and Barthez (1861, R 17) opposed Heine's view. Because of negative results in some autopsies made by them, they affirmed that there was no organic lesion of the nervous system as the basis of this disease. They proposed the name "*Paralysie essentielle de l'enfance*." Bardeleben (1864, B 4a) considered the conclusions of these two men of little value as the examination was limited to the macroscopical findings.



Duchenne of Boulogne (1855, D 25) agreed with Heine regarding the spinal origin of the disease. He pointed out the relation between the paralysis, the degeneration of the musculature, and the loss of electromuscular irritability in cases of traumatic lesions of the cord and reasoned by analogy that the point of departure of these serious paralyses of infancy might also reside in the spinal nervous system. Duchenne père used the term *Paralysie atrophique graisseuse de l'enfance* because of the fatty degeneration of the muscles. Duchenne fils (1864, D 26) supported his father's view and had additional evidence in the fact that medullary changes in the cord had been found in certain cases with a paralytic fatty degeneration of the muscles although autopsies were as yet too few to permit exact localization.

The first to publish a report of a microscopical examination of a case of poliomyelitis was Cornil (1863, C 27) on Charcot's service. The patient, who died of cancer at the age of 49 years, had had infantile paralysis at the age of 2. Cornil found considerable atrophy of the antero-lateral bundles of the cord, especially in the dorsal and lumbar regions, with amyloid bodies in the anterior horns, most numerous in the vicinity of the blood vessels; but he failed, however, to recognize the significance of the absence of ganglion cells, although he described and illustrated this important fact. "On voit une cellule nerveuse, qui est du reste la seule qui montrait cette préparation; mais sur les coupes plus épaisses nous avons vu que les cellules nerveuses étaient intactes et avaient conservé leur rapports normaux." Charcot (C 9), nearly a decade later, comments on the fact that both he and Cornil had completely overlooked the motor-cell lesions!

Although Cornil was the first to publish an account, Laborde had previously observed a similar spinal lesion. The pathological examination of his case had, in fact, been made with Cornil's assistance (Laborde, L 1) and was described, together with that of a second case, in Laborde's Paris thesis of 1864. The anterior and lateral tracts showed a remarkable proliferation of the connective tissue elements but Laborde stated that the ganglion cells of the anterior horns were "parfaitement saines."

The next step was taken by Prevost (P 26) while on Vulpian's service, in 1865. A woman seen in their clinic with cerebrospinal meningitis, had a pes talus paralyticus with complete atrophy of the calf muscles. Vulpian made a diagnosis of "Paralysie infantile" although no history was obtained. Later at autopsy atrophy of the anterior and lateral columns was noted, and also atrophy of the left anterior horn of the

lumbar enlargement and distortion and diminution in the number of ganglion cells. "On n'aperçoit plus le groupe des cellules externes de cette corne; cepedant, dans quelques préparations, on en retrouve encore deux ou trois qui sont déformées, et qui manquaient dans d'autres préparations." Prevost and Vulpian, however, drew no conclusions from their interesting observations, which were confirmed by Lockhart Clarke (J 10) in 1868. Römer (R 25) comments: "These authors, therefore, observed the most important fact and described it, but did not appreciate that it was the one thing by which the occurrence of the paralysis could be explained."

This interpretation was made by Charcot (C 10). In 1870, together with Joffroy, an interne on his service, Charcot published the results of the examination of a woman, of 40 years, who had been paralyzed for 33 years. They reported "an alteration of the anterior horns of the gray substance of the spinal cord, or, more particularly, of the motor nerve cells." Römer describes this event as "work which . . . may be considered as laying the true foundation of all subsequent microscopical pathology." Charcot observed that the lesions, especially in the cervical and lumbar enlargements, were more pronounced in the left half of the cord than in the right, and that atrophy of the muscles and loss of motor power were also more marked in the extremities of the left side. He concluded that there was a correlation between the site of the alterations in the cord and the distribution of the paralyses and inferred that irritation of the ganglion cells transmitted by way of the nerves resulted in trophic lesions of the muscles. The formulation of this important hypothesis was not the only conclusion reached. In the absence of evidence of hemorrhagic or inflammatory changes, and in view of the remarkable localization in the anterior horns, it seemed to him more probable that the motor nerve cells and not the neurologia were the seat of the primary lesion. Moreover it seemed likely that the irritative process did not affect the nerve cells one by one in a progressive manner, as in progressive muscular atrophy, but invaded a large number simultaneously, destroying their motor function at one stroke. Certain cells less profoundly affected than others later recovered their function, and this phase corresponded to the amelioration of symptoms which always occurred at a certain stage of the malady. Charcot called the disease "*Tephromyelitis anterior acuta parenchymatosa*" (C 11).

In the same year (1870) Parrot and Joffroy (P 3) had an opportunity to examine the cord of a 3-year-old child 1 year after the acute illness. In sections in which the ganglion cells appeared normal, the blood



vessels were increased in number with thickened walls and small round cell infiltration; in other sections, however, the ganglion cells were affected although there was no especial change in the blood vessels. Parrot and Joffroy therefore accepted Charcot's conclusion.

Vulpian (V 5) also contributed to the "medullary theory." In 1870, he reported the post-mortem findings on a patient of 66 years who had suffered from a paralysis dating from childhood. In the atrophy of the nerve cells and in the disappearance of many of them, the cord lesions were analogous to those found in similar cases.

Roger and Damaschino were the first to have an opportunity to examine less chronic cases. In 1871, they published three histological studies (R 32) made  $2\frac{1}{2}$ , 6, and 13 months after onset of the disease. They found the characteristic alteration to be a lesion of the cord, more particularly in the anterior portion of the gray matter with marked changes in the vessels and cell proliferation of inflammatory character. Thus these authors concluded that they were dealing with a true, acute inflammation of the cord and raised the question as to whether the primary changes might not be interstitial rather than medullary in character.

The identity of certain paralyses of adults with the spinal paralysis of children had already been recognized on clinical grounds (Moritz Meyer, M 37; Charcot, C 11; Duchenne (de Boulogne), D 25; Kussmaul, cited by Anton Frey, F 64; and others). Gombault (1873, G 14) in Charcot's clinic was the first to confirm these observations with his report of a case "with anatomical lesions approximately the same as in infantile paralysis." This was a woman of 67 years who had suddenly developed 7 years previously a flaccid paralysis of the extremities. The lesion in the cord was confined almost exclusively to the anterior horns; the motor ganglion cells showed all stages of atrophy. The anterior roots were also atrophic. Some degenerated cells were found in the hypoglossal nucleus although no symptoms had been observed that would suggest a lesion in this location. Pathological changes in the bulbar nuclei had not previously been recorded; Roger and Damaschino (R 32) had failed to find the alteration they expected in the trigeminal nucleus in a case that had shown a fatty degeneration of the temporal muscle.

Positive findings in adults similar to those described by Gombault were soon after reported by Petitfils (1873, P 10; observations by M. Lancereaux, microscopic examination by M. Pierret), and later by Erb (1875, E 16), Leyden (1875, L 56), and Schultze (1878, S 19).

Roth (1873, R 55) seems to have been the first German worker after Heine to make any important contribution to the pathology of the disease. Although his case died in the chronic stage, 11 months after onset, Roth found an interstitial myelitis of the lumbar cord, involving the anterior horns and also the posterior horns and white matter. Foci showed atrophy of the nerve fibers and absence of the large, multipolar ganglion cells. He concluded that the primary lesion was interstitial.

Erb (1875, E 16) was at first of the same opinion. Although his work was clinical, rather than pathological, he described the disease as "essentially an inflammatory process of the gray anterior columns . . . an acute interstitial myelitis." Later, however, he (E 17) suggested that the connective tissue and nerve substance might be attacked simultaneously by the irritative process.

Although a few workers (as noted above) had observed some pathological changes in the white matter, in most instances the lesion appeared to be confined to the gray substance. Therefore, as Frey (1874, F 65) has described, in order to distinguish between a *leuko-myelitis* and a *polio-myelitis*, Kussmaul introduced in his clinic the designation *Poliomyelitis anterior infantum*, resp. *adultrum*. Although based on an imperfect understanding of the pathological process, a fact noted by Putnam (P 29) as early as 1883, the name poliomyelitis has been retained and is still the term most frequently used for the disease under consideration.

Ascending paralysis of the Landry type presented many difficulties to the early students of nervous diseases. In 1871 Chalvet (C 7) had performed an autopsy on a case of this form (microscopic examination by M. Kieffer) and reported that the motor cells of the lumbar cord were swollen and yellow in color and that the vessels were distended with a yellow liquid. Thus it was not true, Chalvet pointed out, that all cases of Landry's disease were negative pathologically. Although the findings in this case were not typical of *paralysie spinale aiguë*, it was suggested that some cases of ascending paralysis might prove to be infantile paralysis. Petitfils (P 10) subscribed to this hypothesis, which was later confirmed by Eisenlohr (1878, E 11). The latter found exudate and extravasation of inflammatory nature in a case of ascending paralysis in an adult (aged 42 years) with death in 9 days. This seems to have been the first pathological examination of a case of poliomyelitis made during the acute stage.

In 1880, Eisenlohr (E 13) examined a case of the bulbar type and noted destruction of the ganglion cells of the left facial nucleus. He reported 2 additional cases in the same year (E 12) with death 6 and



13 months after the onset of the disease. These showed myelitis of the gray matter, affecting long stretches of the anterior column; not circumscribed foci but a primary diffuse disease affecting all tissues and the vessels especially. He was opposed to Charcot's view of a primary degeneration of the ganglion cells, and thought that even "interstitial myelitis" was too narrow a term.

Thus, at this period, while details of the pathological process were being accumulated gradually, investigators were divided into opposing groups. Charcot's theory that the process was primarily parenchymatous was supported by the workers in his own clinic and also by Déjerine (1878, D 8), Friedländer (1882, F 69), Stadelmann (1883, S 52) and Rissler (1888, R 18). Others, influenced by Roger and Damaschino, considered the interstitial inflammation primary: Leyden (1875, 1880, L 56, L 57), Schultze (1876, 1878, 1882, 1905, S 18, S 19, S 20, S 22), Eisenlohr (1878, 1880, E 11, E 13, E 12), Taylor (1879, T 3), Turner (1879, T 21), Archambault and Damaschino (1883, A 31) and Damaschino (1885, D 3). A few, as Petitfils, Erb, Déjerine and Huet (D 9) and Drummond took an intermediate stand. Drummond (1885, D 21) reported a case in the acute stage with death from respiratory paralysis 6 to 7 hours after onset. He found congestion, with free leucocytes and minute hemorrhages at the level of the third and fourth cervical nerves. The ganglion cells were swollen. The inflammation was not confined to the anterior horns but spread to the surrounding areas. Drummond concluded that it was "obvious that the several parts affected must take part . . . in the destructive process induced by the inflammation."

During this period, too, the possibility of a vascular origin of the disease was considered. Petitfils (1873) had suggested that the localization of the myelitis in the anterior horns was influenced by the excessive vascularity of this part of the cord. Money (1883, M 41) and Putnam (1883, P 29) both emphasized the presence of a diffuse inflammation. Putnam thought that the original morbid change was one affecting the vessels, and that the median portion of the anterior cornu was especially prone to inflammation and therefore suffered most severely.

The most important work of this period subsequent to that of Charcot, however, was Rissler's study of 3 cases in the acute stage in 1888 (R 18). Although it is not true, as is sometimes stated, that Rissler was the first to describe the pathology in acute cases (see Eisenlohr, Drummond), it is true, as Wickman (W 21) says, that Rissler was the "first to give a comprehensive description of the pathological anatomical

processes of the acute stage." His account of the alteration in the interstitial tissues and vessels of the cord, Wickman calls "classical." Rissler was the first to describe softening of the spleen and enlargement of the solitary follicles and Peyer's patches of the intestine and of the mesenteric lymph nodes. Medin (1891, M 32), who had observed 2 of these cases clinically, also stressed the involvement of the intestinal mucosa and the adenopathy, and noted cloudy swelling of the heart muscle and of the parenchyma of the liver and kidneys. These were findings similar to those known to occur in the severe acute infectious diseases and indicated, Medin thought, that in the acute stage there was an invasion of the entire organism.

Rissler's observations were based upon the examination of 5 cases of poliomyelitis. Three of these patients had died at the end of the first week of their illness. Hyperemia of the dura was noted in 2; and in 1 the pia was also hyperemic. "On microscopic examination it was found that a highly characteristic and uniform disease process had affected the anterior horns of the gray matter of the cord and certain areas of the medulla and pons physiologically similar." The ganglion cells showed a series of changes from granular clouding of the protoplasm to complete destruction. Rissler found nothing in the adjacent or distant neighborhood of the cells that could be considered the cause of the degeneration. However, he described what he called a "form of ganglion cell death, in which other cellular elements, most probably white blood cells, play a prominent part."

In the pericellular spaces there were observed varying numbers of these wandering cells, sometimes "of an indifferent appearance," sometimes bizarre in shape. Rissler described the invasion and gradual destruction of the ganglion cells by these elements and commented that an intensive study of all the possible intermediate forms was required before he could recognize in the indefinite groups of granulations and nuclei what had formerly been ganglion cells.

"But the most striking feature of any section is the marked hyperemia everywhere present and, associated with it, an abnormal exudation." This exudate was, at times, serous and was apparent in a remarkable widening of the lymph spaces. At certain points the lymph sheaths and interstitial spaces seemed to be filled with a peculiar glass-like substance which proved to be made up of the migrated constituents of the blood, especially of white blood cells. In 1 case, the adventitia and lymph sheaths of the larger vessels were literally crammed with leucocytes. Red blood cells were also present; they seemed to have wan-



dered out by diapedesis. Streaks and petechiae that macroscopically resembled hemorrhages proved on microscopical examination to be extraordinarily distended blood vessels. True hemorrhages occurred rarely and could not be, Rissler thought, the causal factor in the disease.

He then discussed the old controversial point as to whether the ganglion cells or the neuroglia were the first to be affected. The general opinion at the time of his writing was in favor of the latter view, but he did not find the greatest degeneration of ganglion cells invariably co-existent with the most marked inflammatory changes. In many instances where the vessel and the neuroglia alteration was of the greatest intensity, the ganglion cells varied greatly in the degree of degeneration. Diseased nerve cells appeared in some places where the lesion in the vessels was least.

Thus Rissler became convinced that Charcot's hypothesis of a primary degeneration of ganglion cells offered the best explanation of the picture. He assumed that when the motor nerve cells were affected by some injurious agent, degeneration followed. At the same time, the causal agent acted perhaps both on the vessels and on the interstitial substance—or perhaps the degenerated ganglion cells produced the reaction. It might be possible that the whole series of changes in the ganglion cells was secondary to the phenomenon above described in which the lymphoid cells were involved.

In addition to these lesions in the anterior horns, Rissler demonstrated an abnormality in the white matter which he thought had not been described previously. This was localized in the antero-lateral columns and consisted in a degeneration of the nerve fibers, which he considered as a secondary degeneration of the association tracts by which the destroyed ganglion cells of definite cord segments were connected with each other.

During the next 15 years, although there were no remarkable developments in the history of the pathology of the disease, a few important observations were recorded. On macroscopic examination, Rissler (1888) had noted, without further comment, hyperemia of the pia in 1 case. Dauber (1893, D 5) first, and Goldscheider (G 13) in the same year, each described pial involvement in an acute case. Infiltration of the pia was later shown by Wickman (W 21) and by Harbitz and Scheel (H 10) to be a constant feature of the acute process.

Atrophy of the cerebral cortex in a case of long standing had been described by Sander (1875, S 4) and later by Rumpf (1882, R 57), Colella (1889, C 18), and Probst (1898, P 27). Redlich (1894, R 2)

was the first to note circumscribed vascular injection in the cerebral convolutions, slight inflammation of the pia and small foci in the basal ganglia and in the centrum semiovale Vieussenii. Wickman (W 21) and Harbitz and Scheel (H 10) later made a careful study of the nature and location of the cerebral lesions.

Degeneration of the diaphragmatic fibers was mentioned by Redlich (1894, R 2) and by Probst (1898, P 27).

Nor were there, during this period, any very valuable contributions to the theories of pathogenesis. Leegard (1889, L 23; cited by Wickman, W 21) endorsed Rissler's support of the hypothesis of the primary degeneration of the ganglion cells. Von Kahlden (1893, 1894, K 3, K 4), too, appeared as an enthusiastic advocate of Charcot's theory. He found a lack of agreement between the ganglion cell degeneration and the destruction of the myelinated nerve fibers which pass through the anterior horns. If the process were interstitial, the alterations in the ganglion cells and the nerve fibers should be parallel, von Kahlden argued. Mönckeberg (1903, M 40) and van Gehuchten (1903, V 1), also believed that the primary lesion was medullary.

Many other writers, however, Schwalbe (1902, S 24), Praetorius (1903, P 25), Schmaus (1905, S 9), Neurath (1905, N 12) and Lövegren (1905, L 61) held the conception previously suggested by Dauber (1893) and Redlich (1894) of a simultaneous injury to the ganglion cells and interstitial tissue.

By means of serial sections, Kawka (1889, K 5), demonstrated a relation between the focal lesions and the vessels. Goldscheider (1893, G 13) by the same method showed that the "choice" of degenerated ganglion cells was not according to cell groups but according to vascular regions. Siemerling (1894, S 41) came to a similar conclusion and emphasized the part played by the anterior spinal artery in determining the distribution of the lesions. Other advocates of the vascular theory followed: Trevelyan (1895, T 17), Bickel (1898, B 12; microscopic examination by Roeder), Matthes (1898, M 30), Wing (1899, W 25) and, especially, Bülow-Hansen and Harbitz (1898, B 38).

Pierre Marie (1892, M 17), influenced by Kadyi's experimental work (Kadyi, H., cited by Wickman, W 21), also thought that the site of the principal lesion was determined by the central artery, but that the pathological process consisted of embolism or thrombosis. Money (1883, M 41), Mott (1899, M 49) and Batten (1904, B 6) each found thrombosis present in one instance, but such cases, as Wickman noted, have been too few to permit a generalization. Wickman (W 21) has



discussed in detail the arguments against this theory and also against "any preponderating influence of the central artery."

The question of a possible portal of entry came up at this time. The first discussion of the subject based on anatomical findings, is found in the report of Bülow-Hansen and Harbitz (1898, B 38). These authors expressed regret that so little had been reported with regard to the pathology of other organs than the brain and cord and suggested that the gastro-intestinal tract might be the portal of entry; the cases of Medin and Rissler and the 2 examined by Bülow-Hansen and Harbitz presented important intestinal changes and the patients had had symptoms of gastro-enteritis; Dauber's case showed an inflamed tonsil and an enlarged cervical lymph node, and in this instance too the onset had been accompanied by vomiting and diarrhea.

In 1905, appeared the first of a series of studies by Ivar Wickman (W 20). Römer (R 25) refers to Wickman's work as "of extreme importance, not only because of its extent (7 acute cases, 3 of Rissler's cases re-examined, and 2 cases during convalescence) and its thoroughness of description, but also because of the expert critical analysis of all the vexed points in the pathology and pathogenesis of the disease. Wickman raised the question, *really* for the first time, of the point of entrance, the method of infection, and of the spread of the virus." In 1909 (W 22) a study was made of 7 more acute cases. A complete discussion of the subject appeared in Wickman's monograph (W 21).

The following has been taken freely from Wickman's description of the pathology of the disease. The symptoms of poliomyelitis are due to an inflammatory process in the central nervous system. The inflammation is not confined to the spinal cord, but occurs in the medulla, pons, cerebellum, cerebrum and meninges and involves both the gray and the white matter and the pia mater.

The pia is the seat of round-cell infiltration. In the spinal cord the process is most intense in the anterior horns of the cervical and lumbar enlargements. The interstitial tissue and the vessels are most severely affected. There is no evidence of thrombosis or embolism. The cellular exudate is important. The infiltration of the adventitia is most marked around the entrance of the central vessel at the bottom of the anterior fissure. The arteria centralis is not so severely implicated. The veins are more seriously affected than the arteries. Round cells (derived from the vessels) penetrate the surrounding tissue and enclose the vessels like a wall. The round cells represent a further stage in the development of the lymphocyte (Maximov's polyblasts). The posterior horns show analogous alterations.

The edema is important clinically and may be the explanation of the rapid disappearance of the paralysis.

Degeneration of the ganglion cells has never been observed in man in the absence of interstitial lesions, although the opposite condition is sometimes present; the degree of degeneration is usually in direct relation to the intensity of the interstitial inflammation.

In his discussion of pathogenesis, Wickman stated "that no parenchymatous process can adequately explain the known changes in man" but "that the apostles of the inflammatory nature of the malady do not attempt to deny the direct action upon the ganglion cells. . . . In man, many factors undoubtedly point to the interstitial, as the more important changes" but "I call attention to the undeniable possibility of a direct inflammation upon the nerve tissue. . . . Many pathologists, however, believe that here, as elsewhere, it is immaterial whether an inflammation is discernible first in the parenchyma or not. The essential points to be determined in either case are the same: First, why the malady, which from a pathological standpoint is a strictly localized affection, develops clinically as a systemic disease; and second, why the effects are limited practically to the anterior horn, and are not distributed as in a transverse myelitis."

In his earliest work, Wickman stated his conviction "that the specific pathologic changes could best be explained as a lymphatic infection." Later he felt that experimental work on monkeys had confirmed his hypothesis and that "the virus spreads from the site of inoculation especially by way of the nerves; the infection extends along the lymphatics, which accompany the nerves." With regard to the portal of entry in human beings, this author expressed his "belief that human infection takes place by way of the alimentary canal."

Wickman's work overlapped in time that of two other important groups of investigators: Forssner and Sjövall (1907) and Harbitz and Scheel (1907). Forssner and Sjövall (F 59) were the first to report inflammatory lesions in the spinal ganglia, a finding later confirmed by Strauss (1910, S 62, S 63) and also noted in the experimental disease by Flexner and Lewis (1910, F 42).

Forssner and Sjövall also recorded that they had observed neuronophagia in abundance. They felt that this phenomenon was the expression of a true phagocytosis.

The Norwegian epidemics of 1903–1906 afforded an unusual opportunity for the study of pathological material. Harbitz and Scheel (H 10) studied 17 cases, 13 during the acute stage and 4 in a later stage. Amoss (A 14) found their observations sufficiently valuable to say: "The



development of the pathology of acute poliomyelitis rests upon the work of Harbitz and Scheel." Their conclusions differed from those of Wickman in that they believed that the virus reached the pia by way of the blood and that the inflammation then spread out from the pia along the vessel sheaths into the substance of the nervous tissue. A meningitis was therefore primary. The localization was determined by the central vessels in the anterior fissure.

With the production of experimental poliomyelitis in monkeys (Landsteiner and Popper, 1908; Knoepfelmacher, 1909; Flexner and Lewis, 1909; Leiner and von Wiesner, 1909; Landsteiner and Levaditi, 1909; Römer, 1909; Strauss and Huntoon, 1910) came new opportunities for the study of the pathological changes of poliomyelitis in the acute stage, and of the distribution and spread of the virus within the organism. As evidence of the successful transmission of this disease to monkeys Landsteiner and Popper (1908, L 10), demonstrated sections of the human cord from which the first virulent emulsion was derived and sections of the cords from the 2 monkeys that had developed the experimental disease. The histological findings in the monkey cords showed typical poliomyelitis agreeing with the human picture. When Flexner and Lewis (1909, F 39) succeeded a year later in transmitting the disease in series by intracranial inoculation, they also found that "microscopic study of the spinal cord from the affected monkeys showed, without exception, lesions similar to those of poliomyelitis in man."

A discussion of routes of inoculation and of the distribution of the virus within the body as shown by inoculation tests is included in the *Chapter on Etiology*. Reference will be made in this chapter only to that part of the experimental work which bears directly on the pathology or pathogenesis of the disease.

### PORTAL OF ENTRY

The fact that the experimental disease could be produced by the nasopharyngeal and tracheal routes and that the virus could be demonstrated in the nasal mucosa of human beings and of monkeys after intracerebral inoculation; in the olfactory lobes, after inoculation of the nasal mucous membrane; in the tonsils, in both the human and experimental disease; and in the nasal secretions of human beings and of monkeys, inoculated intracerebrally, suggested, as first pointed out by Flexner and Lewis (1910, F 42), that the nasopharyngeal mucosa was the path of entry and also the path of elimination of the virus. The view that the upper respiratory mucous membrane would, under usual conditions, be the most frequent atrium of infection in the human dis-

ease and the site from which it could readily pass by way of the filaments of the olfactory nerve to the olfactory lobes of the brain and thence to the medulla and cord has been held consistently by Flexner and his associates (Flexner, Peabody and Draper, F 51; Flexner and Clark, F 34; Flexner and Amoss, F 21, F 22, F 27; Amoss, A 18) and is widely accepted at the present time (Müller, 1925, M 55; MacAusland, 1927, M 1; Marinesco, Manicatide, and State-Drăganescu, 1928, 1929, M 18a, M 19; Lange, 1930, L 13; Stimson, 1931, S 61; Erb, 1931, E 15; Stallybrass, 1931, S 53).

Many authors, however, have felt that there was evidence to show that the virus may also gain access to the body by way of the digestive tract. As previously mentioned, Bülow-Hansen and Harbitz (1898) were the first to suggest this possibility and Wickman concluded that the gastro-intestinal was the more probable route of infection in man. In an epidemic in Westphalia, Krause (1909, K 32) reported that in 90 per cent of the cases the onset was marked by gastro-intestinal disturbances. In 8 fatal cases autopsy showed a striking change throughout the intestine, especially of Peyer's patches and of the solitary follicles; the alterations were most marked around the ileocecal valve; the mesenteric nodes were markedly swollen; a splenic tumor was also noted. Krause concluded that epidemiological, clinical and pathological findings indicated that the intestinal tract is the portal of entry. Dahm (1909, D 1) noted a similar involvement of spleen, mesenteric nodes and lymph follicles in 3 autopsies and suggested, as did Strauss (1910, S 62, S 63), Leiner and von Wiesner (1910, L 28, III), and Römer (1911, R 25) that the virus might enter the body through the nasopharynx or the intestinal tract or both; Römer thought that this varied in different epidemics. Because of the intestinal lesions and turgid mesenteric nodes in 3 cases, Webster (1919, W 7) also suggested an intestinal atrium of infection and attempted to confirm his idea experimentally. He was unable, however, to demonstrate the virus by injecting a monkey intracerebrally with an emulsion of lymph gland taken from a particularly swollen group of the mesenteric nodes. Smith (1932, S 48) has recently made an unsuccessful attempt to recover the virus from isolated lymph nodes, bits of spleen, and loop of ileum in human cases although pronounced lesions were present in these locations. Evidence in favor of invasion through the alimentary canal (the tonsils are included by some writers as the upper portion of the digestive tract) has also been found by Kling (1928, K 11), Kling, Levaditi and Lépine (1929, K 13), Burrows (1931, B 43), and Toomey (1932, T 16).

After passing through the digestive mucosa, according to Kling,



Levaditi and Lépine (1929, K 13), the virus travels toward the central nervous system along the "filets" of the abdominal sympathetics. They consider it probable that the virus first reaches the neurons of the visceral ganglia of the neuro-vegetative system and then passes along the axons toward the rami communicantes, the spinal ganglia, roots, and anterior horns. This hypothesis would have a greater value if lesions could be found in the micro-sympathetic ganglia in the wall of the intestine (Marinesco, Manicatide, and State-Drăganescu, 1929, M 19). But apart from degenerative lesions of certain sympathetic cells and of a certain number of satellite cells, the Rumanian workers were unable to find marked alterations in these ganglia which would constitute the first step in the propagation of the virus along the nerve filets to the cord. From a study of 134 autopsy cases in New York City in 1931, Smith drew the conclusion that the lymphoid tissue of the lower ileum and the adjacent lymph nodes were the "first to show evidence of the disease. The Peyer's patches were enlarged and injected and in many instances actually ulcerated." It seemed to him, therefore, "that the gastro-intestinal tract is probably the usual portal of entry of the infection."

Experimentally, the virus is introduced by inoculation into monkeys much more readily by way of the nasopharynx than by way of the alimentary canal (see *Routes of Inoculation, Chapter on Etiology*). Specific lesions have not been demonstrated either in the nasopharyngeal or in the intestinal mucosa of human beings that have died in the acute stage of the disease. There is often evidence of involvement of the upper respiratory mucous membrane. The character of the intestinal lesions noted is markedly involved in some instances and in others is only mildly affected. To many authors, such lesions are evidence of a portal of entry while others look upon them merely as a part of a general lymphatic hyperplasia and still others (Flexner, 1912, F 37; Kling and Pettersson, 1912, S 67; Marinesco, Manicatide and State-Drăganescu, 1929, M 19) as the result of swallowed virus. Von Wiesner (Z 3) called attention to the fact that such sites of inoculation as the nasal and intestinal mucous membranes or the peripheral nerves in monkeys artificially infected by these routes do not show any noteworthy changes; thus the natural point of entry of the virus may not be marked by specific pathology. Marinesco and State-Drăganescu (1931, M 20) too have stated that absence of inflammatory lesions at the site of the portal of entry and in the nerves does not permit the study of the probable course of entry of the virus. The symptoms of onset

in the human disease vary in different epidemics. Moreover, neither the upper respiratory nor the gastro-intestinal symptoms serve to distinguish poliomyelitis from other acute infections. Thus it would be difficult to draw a conclusion with regard to the path by which the virus enters the body from these features. To Wickman (1911, W 21), however, the ascending order of the development of the paralyses and the fact that the lower extremities were more frequently involved than the upper was significant of invasion through the alimentary canal. Leiner and von Wiesner (1910, L 28, II and III) concluded from their experimental work that the order of appearance of the paralyses was dependent on the site of the original infection and that the virus reached the cord by the shortest path. After infection by way of the upper respiratory mucosa in monkeys paralysis developed first in the anterior half of the body; infection by way of the gastro-intestinal tract resulted in paralysis of the posterior extremities; on intraneural inoculation (median or sciatic nerve) the corresponding extremity was the first to become paralyzed. Römer (1911, R 25), however, pointed out that after intracerebral inoculation the legs became paralyzed first, the contralateral limb before the homolateral, then the arms, and then the respiratory muscles. A similar sequence has been described by Fairbrother and Hurst (1930, F 6) with the conclusion "that the symptomatology in human cases cannot be accepted as evidence of entry of the virus by the intestinal tract."

### ACUTE STAGE AND PATHOGENESIS

Most students of poliomyelitis since the time of Wickman have agreed that the virus travels from the point of entry in the human disease, or the site of inoculation in the experimental disease, by way of the lymphatics along the nerves (or the lymph spaces surrounding the blood vessels, Landsteiner and Levaditi, L 34) to the central nervous system (Leiner and von Wiesner, L 28, III, Z 3; Römer, R 25; Peabody, Draper and Dochez, P 7; Abramson, A 4). Moreover, there is not only a lymphocytic reaction within the central nervous system, but there is hyperplasia of the lymphoid tissue throughout the body. Neurath (1905, N 12) described a case with hyperplasia of the thymus, of both tonsils, of the follicles of esophagus and intestine, and also of the lymph nodes, especially the cervical and mesenteric, and with moderate enlargement of the spleen. Von Wiesner (1911, Z 3) noted hyperplasia of the entire lymphatic system, usually including the thymus, as an almost constant feature in his cases. As similar findings have been described in other



infectious diseases and are therefore not specific for poliomyelitis, they have usually been interpreted as evidence of a systemic infection (Medin, 1891, M 32; Flexner, 1911, F 12; Kling, Pettersson and Wernstedt, 1912, S 67; Peabody, Draper and Dochez, 1912, P 7; Abramson, 1918, A 4; Smith, 1932, S 48). Recently, Burrows (1931, B 43), however, has gone so far as to say that involvement of the central nervous system is to be regarded merely as a complication of a systemic disease, and that poliomyelitis "is not a primary disease of the central nervous system; it is a disease of the lymphatic systems of the body." He has even suggested that the name be changed to "acute lymphatic hyperplasia."

Von Wiesner (1911, Z 3) had another interpretation. In his cases he found no evidence of local inflammatory swelling. A pronounced hyperplasia of the lymphatic system was present not only in acute cases but even in a case examined over a year after the original infection. Von Wiesner thought that in these cases one might be dealing with individuals of a lymphatic constitution and that such persons might succumb more readily to poliomyelitis. According to Symmers (1918, S 68; personal communication), infections in general are very apt to run a rapidly fatal course in subjects of status lymphaticus. Moro (1931, E 6) and Smith (S 48) have made somewhat similar statements to the effect that poliomyelitis, as well as other infectious diseases, occurs more frequently in individuals of the lymphatic type. In a study of a large group of cases of poliomyelitis, Smith found that the thymus was unusually prominent and averaged from 10 to 20 per cent more in weight and was correspondingly larger in size than in such diseases as measles, scarlet fever, and diphtheria.

The course taken by the virus within the central nervous system has not been traced with ease. According to Harbitz and Scheel (1907), a meningitis was primary; the inflammation spread from the pia along the vessel sheaths into the substance of the cord. Many other writers have accepted the theory of a meningeal spread: Strauss (1910, S 62, S 63), Schreiber (1911, S 11), Müller (1925, M 55), Marinesco, Manicattide and State-Drăganescu (1929, M 19). The Rumanian authors suggested a second path of transmission along the vessels of the ependymal cavities. The meningeal reaction and the rôle of the spinal fluid in the distribution of the virus have been emphasized particularly by Flexner and Amoss (1914, F 21, F 22), Spatz (cited by Pette, P 11) and Amoss (1928, A 18).

Wickman (1911, W 21), differed somewhat from Harbitz and Scheel

and stated that "microscopic examination fails to substantiate that the inflammation, as a rule, diffuses inward from the pia." He thought as have many others, that diffusion of the virus within the cord and its membranes followed the lymph channels. Von Wiesner (1911, Z 3) concluded that the pial infiltration was secondary to changes in the anterior horns. His examinations showed, as was noted also by Walter (1912, W 3), that the intensity of the perivascular infiltration diminished from the center toward the periphery. Von Wiesner thought that the process began with destruction of the ganglion cells (due perhaps to some chemical affinity between the virus or its toxin and the anterior horn cells) and spread up and down the cord by the lymphogenous route. Römer (1911, R 25) thought the virus entered the cord by way of the spinal roots and then spread along the lymph spaces around the veins, or in those that lie within the nervous tissue.

Recent experimental work has led several groups of investigators to support a different theory. Pette (1930, P 11) does not concede to the spinal fluid or lymphatic route more than a minor share in the distribution of the virus. Hurst, together with Fairbrother, (1929, 1930, H 39, F 6, H 40) has arrived at a similar conclusion. Their studies as well as the experiments of Jungeblut and Spring (1930, J 28) have shown that the main spread of the virus may be due to axonic transmission, though the cerebrospinal fluid may be a contributory factor.

In order to give a complete picture of the morbid anatomy of poliomyelitis, as observed both in human beings and in monkeys, together with the argument on pathogenesis, it seems desirable to quote at length from two outstanding groups of workers, whose observations, while in agreement on many points, have led them to different conclusions. It must be remembered that conclusions drawn from fatal human cases, must, necessarily, be based on the conditions obtaining in the *terminal* stages of the disease, and attention has seldom been paid to the precise mode of development of lesions, which can be followed from the incubation period onward in the experimental animal.

In the United States, the group of workers at the Rockefeller Institute has carried out the most extensive investigation of experimental poliomyelitis and has had opportunity also to observe the human disease, especially during the New York epidemics of 1907 and 1916.

While making a clinical study of acute poliomyelitis, Peabody, Draper, and Dochez (P 7; see also Flexner, Peabody and Draper, F 5) examined autopsy material obtained from 11 human cases that died during the acute stage. They consider it "probable that infection fre-



quently gains access from the upper respiratory tract," and that the virus enters the body by the lymphatics which pass outward with the filaments of the olfactory nerve. The first effect is upon the meninges. "The earliest change . . . is hyperemia and the collection of numbers of small mononuclear cells, probably lymphocytes, in the perivascular lymph spaces of the blood-vessels of the leptomeninges. These lymphatic spaces surrounding the vessels are anatomically processes of the arachnoid spaces, and the lymph in them is in communication with the cerebrospinal fluid. This first change, then, is an acute meningitis. . . . It is usually most marked on the anterior surface of the spinal cord, and especially in the anterior fissure, from which the larger vessels enter the cord. . . . The blood supply of the cord is derived from the vessels of the meninges, and with the advance of the pathological process, this perivascular infiltration follows along the vessels as they enter the cord from the meninges. Thus the earliest change that is found in the cord itself, both in human beings and in the experimentally produced disease, is hyperemia and the collection of small round cells in the lymph spaces surrounding the vessels. This cellular exudate forms a sheath apparently completely surrounding the vessels for long stretches, and in many places the cells are so numerous that they form thick collars which seem to press on the lumen, and thus exert a mechanical effect in obstructing the circulation. While the cellular exudate is in the outer part of the vessel wall, it is probable that there is often some effect, either toxic or mechanical, on the internal lining of the vessels, for hemorrhages, minute or extensive, are frequent findings, and one of the most prominent features of most cases is the extensive edema. These three factors, cellular exudate, hemorrhages, and edema, all of them dependent on vascular changes, may perhaps be regarded as the primary reaction of the nervous system to the virus of poliomyelitis. The effects produced on the nerve cells themselves are probably either dependent on these vascular disturbances or they may be due to a direct action of the virus. This superior importance of the vascular system in determining the nervous lesions has for a long time explained the fact that the cervical and lumbar enlargements of the cord are most affected, and that the anterior horns of the gray matter are more involved than the posterior horns or the white matter. These are, of course, the regions of the spinal cord to which the blood supply is most abundant. . . . It is quite impossible to exclude the fact that the virus may exert some directly toxic action on these (nerve) cells, but in many ways, the clinical and anatomical pictures are readily explained

by the presence of the circulatory disturbance and of the exudate. On such an hypothesis the damaging effects can be assumed to result in part from the direct pressure on the nerve cells of hemorrhages, edema and exudate. There is also the additional factor of anaemia following the constriction of the blood-vessels by the same mechanism. On account of this pressure and anaemia, the nerve cells degenerate. If the hemorrhage and exudate are absorbed soon enough, the cells may recover their function. If, on the other hand, the anaemia and pressure have been prolonged or excessive, the nerve cells go on to complete necrosis. Histological examination shows nerve cells in all stages of degeneration. . . . A most striking picture is formed by the entrance of polymorphonuclear neurophages into the necrotic nerve cells. . . . These changes, most prominent in the anterior horns of the gray matter, are not sharply circumscribed, but are scattered more or less diffusely through both the gray and white matter of the cord.

"The same sequence of changes, vascular disturbance, and subsequent degeneration of the nervous elements, is found to a less degree in the brain, medulla, and pons. Hyperemia and a moderate amount of cellular infiltration may be found in association with the vessels of the cerebrum and cerebellum, but lesions extensive enough to produce motor symptoms are exceedingly rare . . . .

"Of practically constant occurrence are the lesions in the posterior root ganglia. The histological changes are similar to those that take place in the cord itself . . . . These lesions in the sensory ganglia may in part account for the pain which is such a constant feature of the acute stage of the disease. Another element in the production of pain is the cellular filtration which is found along the nerve roots.

"The changes which are found in other organs in acute poliomyelitis are less striking than those in the nervous system, but they have been, in our experience, practically as constant. In all of the 11 acute cases which we have been able to examine, there has been more or less extensive involvement of the lymphoid tissue and of parenchymatous organs. The lymphoid tissue throughout the body appears to react to the virus. The Peyer's patches of the intestine and the mesenteric lymph glands show perhaps the most marked acute swelling. . . . There is also definite, and sometimes pronounced enlargement of the substernal, bronchial, cervical, axillary and inguinal lymph glands and of the tonsils. The spleen is frequently somewhat enlarged, and on section the Malpighian corpuscles stand up in raised, pale, obviously translucent nodules. The thymus shows changes identical with those



in the lymphoid tissue elsewhere. . . . On histological examination some of the lymphoid nodules may present a normal appearance, but the majority consist of a zone of lymphocytes surrounding a more or less sharply circumscribed pale center. . . . In general, necrosis is a more prominent feature in the centers of the lymphatic nodules, and proliferation in the lymph sinuses.

“Among the parenchymatous organs, ‘cloudy swelling,’ such as has been frequently described, is usually met with. In the liver, however, there are other more striking changes. . . . They are for the most part sharply circumscribed areas, ranging in size from lesions which consist of one or two cells to others which include nearly one-eighth of a liver lobule, in which degeneration of liver cells and infiltration of lymphoid cells and polymorphonuclear cells have taken place. . . . The lesions are apparently closely associated with the blood vessels, and while chiefly with the portal vein, they are also associated with central or sublobular vessels . . . .

“That these changes in the lymphoid tissues and in the liver are, in fact, a part of the reaction of the body to the virus of poliomyelitis, would seem to be made certain by the fact that exactly similar lesions may be found in the organs of monkeys which have been experimentally infected with the disease (Flexner, 1911, F 12).

“The disease must be regarded as a generalized process which affects parenchymatous organs, lymphoid tissue, and more especially the nervous system.

“The living virus may come to rest for a time in organs outside the central nervous system to which it is conveyed by the blood. . . . The finding of the virus in the tonsils and nasal mucosa with as great constancy as in the nervous system indicates that these organs play a part in the conveyance of the virus into and away from the central nervous system.”

After intranasal inoculation it was demonstrated (Flexner and Clark, 1912, F 34) that in the experimental disease, “the virus of poliomyelitis passes from the nasal mucous membrane to the olfactory lobes and adjacent parts of the brain before it reaches the medulla or cord. This distribution is what we would expect were the ascent by the direct lymphatic path and not by the blood stream. Were the dissemination by the latter route we should expect early localization in those parts of the cord and medulla that possess an especial affinity for the virus.”

Pathological effects of the action of the virus were observed also (Flexner, Clark and Amoss, 1914, F 36) in the Gasserian and abdominal

sympathetic ganglia. "The histological lesions in the ganglia correspond accurately with those in the spinal cord—partly interstitial, partly parenchymatous. . . . The degree to which the nerve cells are destroyed is variable. The changes in the spinal ganglia appear to arise through an extension of the cellular invasion from the subarachnoid spaces of the spinal cord. The changes in the Gasserian are less severe than those of the spinal ganglia and the mode of invasion is not so evident. The cellular accumulations within the abdominal ganglia (solar plexus) are least marked and so constantly perivascular that infection by way of the blood is indicated. The nerve cells exhibit the slightest lesions of all the ganglia studied . . . .

"Nor does the virus possess a special affinity for nerve cells as such—the lesions affect nerve cells and non-nervous elements within the nervous organs almost indifferently."

At the same time, Clark and Amoss (1914, C 13) repeated the successful inoculation by the intraspinal route as previously reported by Flexner and Lewis, and concluded that "the constant involvement of the pia-arachnoid membranes in poliomyelitis, even when no paralysis occurs, and the fact that infection can readily be produced by intraspinal inoculation suggests anew that in the pathogenesis of poliomyelitis, interstitial tissue changes within the meninges, blood-vessels and ground-substance play a determining part."

Flexner and Amoss (1914, F 21, F 22) published another article with further important conclusions: "The virus of poliomyelitis introduced into the blood may pass indirectly by way of the spinal fluid to the interstices of the central nervous organs."

"To reach the spinal fluid the virus must first penetrate the barrier of the choroid plexus, which operation requires time. By the inoculation test, no virus was detected in the fluid at the expiration of forty-eight hours, only small amounts at the expiration of seventy-two hours, while at the expiration of ninety-six hours the virus had passed more freely. The virus was still detectable in the fluid at the onset of paralysis nineteen days after the intravenous injection.

"Pathological conditions of the lepto-meninges and the cerebro-spinal fluid play an important part in the pathogenesis of epidemic poliomyelitis."

A series of experiments was described which showed that, although the spinal cord and brain have a special affinity for the poliomyelitis virus, infection does not develop after intravenous injection unless some change has "taken place in the structures (vascular or secretory)



that preside over the production of the cerebrospinal fluid." But if an aseptic meningitis was produced by the injection of sterile horse serum, the permeability of the meninges was increased and infection resulted.

A comparison of the lesions in the meninges, spinal cord, medulla and pons, cerebrum and intervertebral ganglia in monkeys after intravenous injection with those resulting from other modes of inoculation showed that, in the former case, the vascular involvement was, in several instances, unusual in extent and infiltrative lesions were present in the choroid plexus. Such a widespread vascular involvement had not been observed in human cases.

The authors then formulated a statement as to the pathogenesis of poliomyelitis: "It is now sufficiently obvious that the virus possesses affinity for nervous tissues in general, but for no element of these tissues in particular. The constancy with which meninges, blood-vessels, interstitial parts, and nerve cells are affected indicates that they all react to the presence of the virus. On the basis of actual observations it cannot be stated that virus is attracted by the nerve cells, either alone or necessarily in advance of the other structures mentioned; while the experiments here recorded show that it is only when the virus is brought to the nervous organs otherwise than by the general blood that the tissues composing them are able to readily remove and attach it to themselves . . . .

"It may be regarded as established that all intraneural means of infection are successful, and that the virus travels with more or less ease and certainty along the nerves to the interstices of the central nervous organs, probably utilizing the lymphatic channels of communication. . . . The central nervous organs, excepting the intervertebral ganglia, are incapable of removing the virus from the general blood prior to changes induced in the blood vessels and in the choroid plexus. They indicate, also, that in the monkey these preliminary lesions are of a nature that permits of differentiation from the lesions caused by the intraneural modes of infection. The lesions in human cases of poliomyelitis would seem to correspond with those caused by intraneural and not by intravenous inoculation . . . .

"In the main, under natural conditions, it is the upper respiratory mucous membrane that would most often become contaminated with the virus, and most readily favor its conveyance to the brain. This series of events is determined by the manner in which the virus is thrown off by the infected body, by the fact of its presence upon the nasal mucosa, even in healthy persons in contact with cases of poliomyelitis,

and by the demonstration that it passes, on the whole easily, along the olfactory nerve fibers to the brain, medulla, and spinal cord. Although the virus is conveyed to the nervous organs from without by the lymph, the distribution throughout the nervous system is, in large part at least, effected through the medium of the cerebrospinal fluid. Even when the virus passes from the blood into the nervous organs, it takes the indirect course through the cerebrospinal fluid . . . .

"Thus the experimental evidence, which is upheld by observation in human cases of poliomyelitis, supports the view that epidemic poliomyelitis is caused by the entrance into the body of its specific microbic cause or virus, through the upper respiratory mucous membrane to the olfactory lobes of the brain, from which by means of the cerebrospinal fluid it is distributed throughout the substance of the nervous organs; but, since the virus may reach the brain by way of any nervous channel, and even, although with great difficulty from the blood, it is, of course, possible that in exceptional instances other modes of infection may arise."

The chapters on poliomyelitis written by Amoss (1928) in Tice's *Practice of Medicine* (A 14) and in *Filterable Viruses* (A 18; R 19) are in essential agreement with the statements taken from publications by various members of the Rockefeller group. In fact Amoss quotes from the 1914 article by Flexner and Amoss (F 22) previously referred to, so it may be assumed that these authors have not changed their opinion in regard to pathogenesis and still hold that the spinal fluid plays the chief rôle in the distribution of the virus within the central nervous system.

During the past 4 years (1928-1932) a series of investigations on the histology and pathogenesis of experimental poliomyelitis has been conducted by Hurst and Fairbrother of the Lister Institute (H 39; F 6; H 40; H 43).

As a first contribution, Hurst (1929, H 39) studied the histology of the experimental disease in the light of modern advances in neuropathological technic. The entire nervous systems of 18 monkeys (*M. rhesus*) infected by the intracerebral route were examined. Three strains of virus were used, the A.M., Ay and Fl.; 15 of the animals were etherized and material obtained immediately. The following summarizes his description.

During the stage of advancing paralysis, lesions in the spinal cord are most marked in the lumbar and cervical enlargements, where nerve-cell destruction is at a maximum, but no level escaped severe damage.



In the early stages pial infiltration is insignificant and confined to a slight excess of cells in the deeper part of the anterior fissure or around the vessels of this region, to the entry zone of the posterior nerve roots, or to the meninges over the posterior septum; in distribution it does not necessarily correspond with areas of most marked change in the gray matter. Intense and widespread infiltration of the pia is found only during the period when the overcharged perivascular spaces of the gray and white matter pour into the pial meshes their surplus cells, which first make their appearance at the points of exit or entry of the vessels. The cells belong mainly to the lymphocytic series; in the earlier stages some polymorphonuclear leucocytes occur and at all stages some endothelial cells are found.

In the cord proper, vascular congestion is always prominent; the cellular lesions fall into the following categories: (1) perivascular and extra-adventitial infiltration, (2) diffuse and focal infiltration of the nervous tissues, (3) destruction of the nerve cells and their fibers.

(1) Limited more or less to the gray matter in the earlier stages, perivascular infiltration around both arteries and veins very soon spreads to the vessels running radially through the white matter and in the anterior fissure, and so reaches the surface of the cord. It is not necessarily present, however, even with the most extreme nerve-cell destruction; frequently, especially with the most virulent strain of virus, it appears insignificant in comparison with the damage sustained by the neurons. It is always predominantly mononuclear, with a high percentage of cells of the lymphocytic series and a variable proportion of adventitial and endothelial elements, but at an early stage and with the more virulent strains, polymorphonuclear leucocytes are numerous and account for perhaps 10 per cent of the total cells. Cells closely resembling the mononuclear leucocytes of the blood, occasional eosinophils, but never plasma cells, have been observed at this stage.

Extra-adventitial infiltration is rarely marked, amounting usually to no more than a slight concentration around a vessel of the cells forming the nervous infiltrate; there is little tendency for the perivascular infiltrate to overflow into the nervous tissues and only when it is very intense do a few cells appear to lie outside the adventitia.

(2) Under a low power, tissue infiltration manifests itself as a diffuse cellular increase in the gray matter of the anterior horns, in the gray commissure, and often over a large part of the posterior horns; numerous focal accumulations of cells also occur. With a higher power, some of the latter are seen to correspond in position with dead or severely



PLATE I  
EXPERIMENTAL POLIOMYELITIS

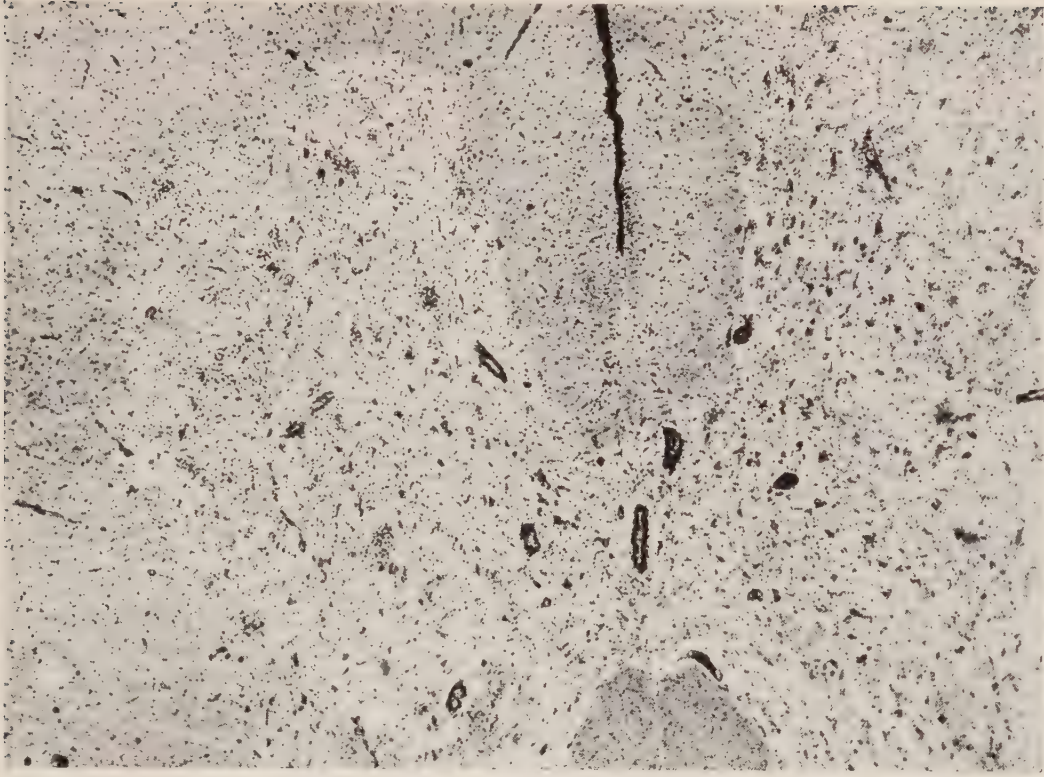


FIG. 1. *Spinal cord.* Mild perivascular infiltration. Small foci of neurophages around damaged nerve-cells of the anterior horns (above). Iron-alum haematoxylin and van Gieson. (Hurst.)

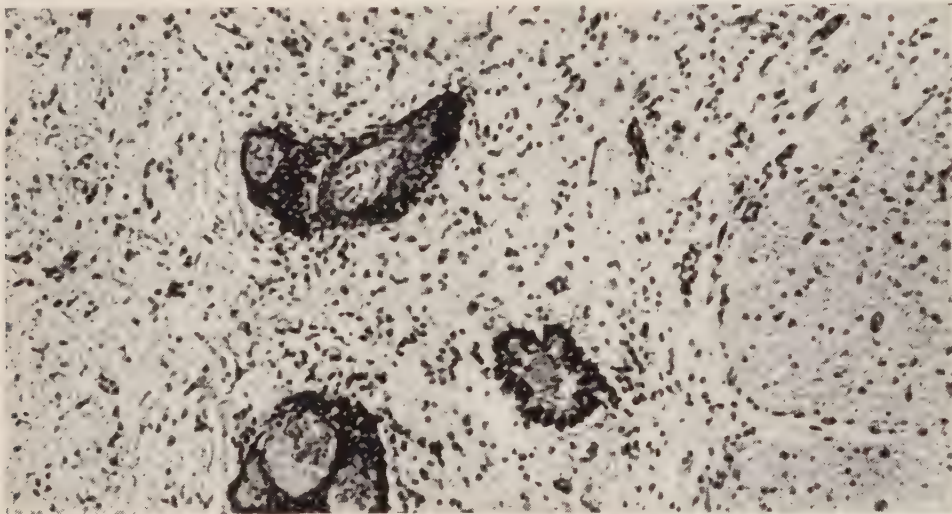


FIG. 2. *Spinal cord.* Perivascular infiltration around central vessels. Iron-alum haematoxylin and van Gieson. (Hurst.)

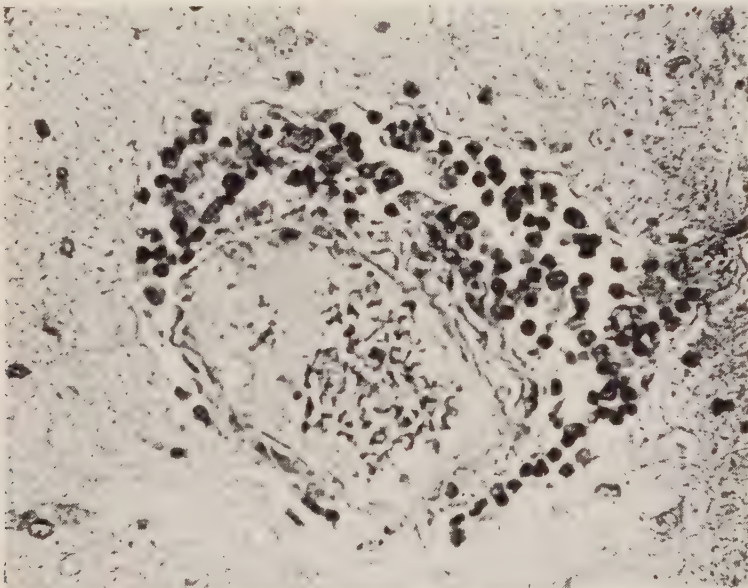


FIG. 3. *Spinal cord.* Perivascular infiltration around central vessel. Panchrom. (Hurst.)





PLATE II  
EXPERIMENTAL POLIOMYELITIS

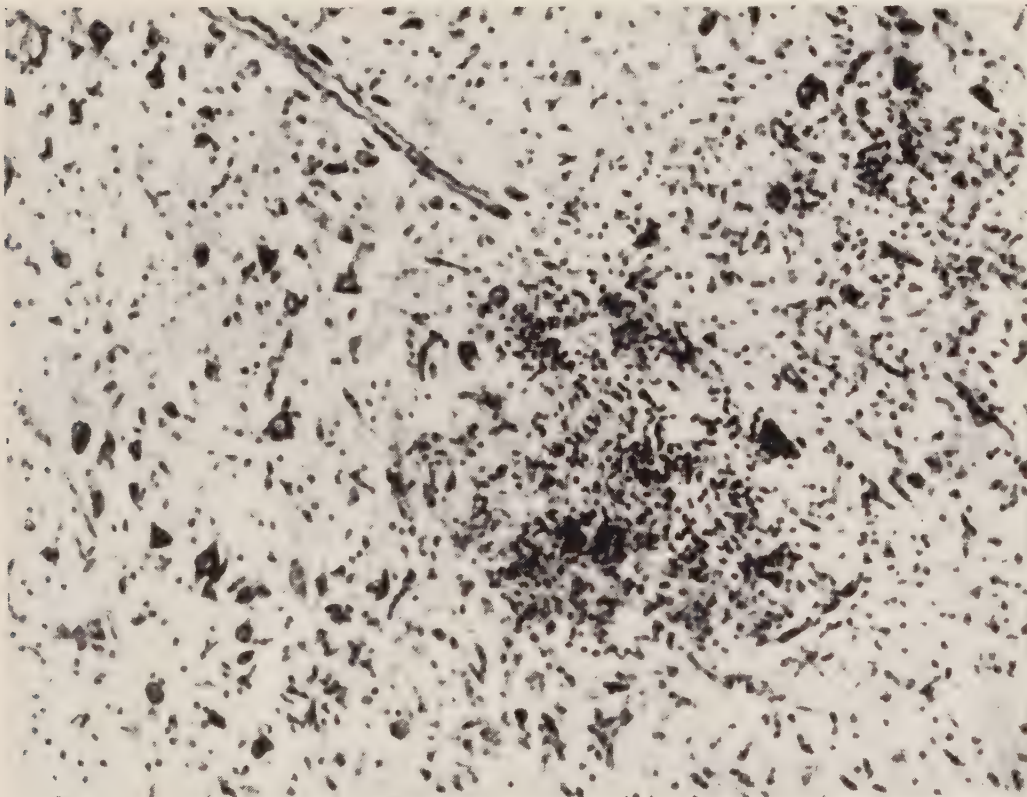
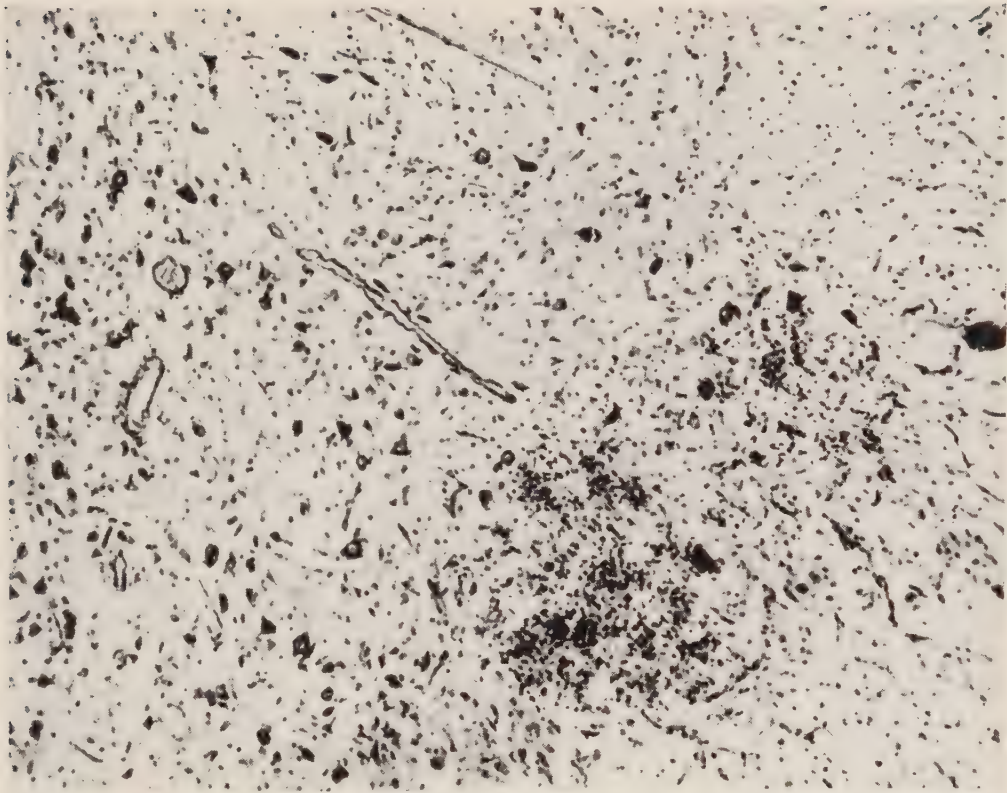


FIG. 4. *Spinal cord.* Areas of diffuse and focal infiltration in anterior horn.  
Nissl. (Hurst.)





PLATE III  
EXPERIMENTAL POLIOMYELITIS

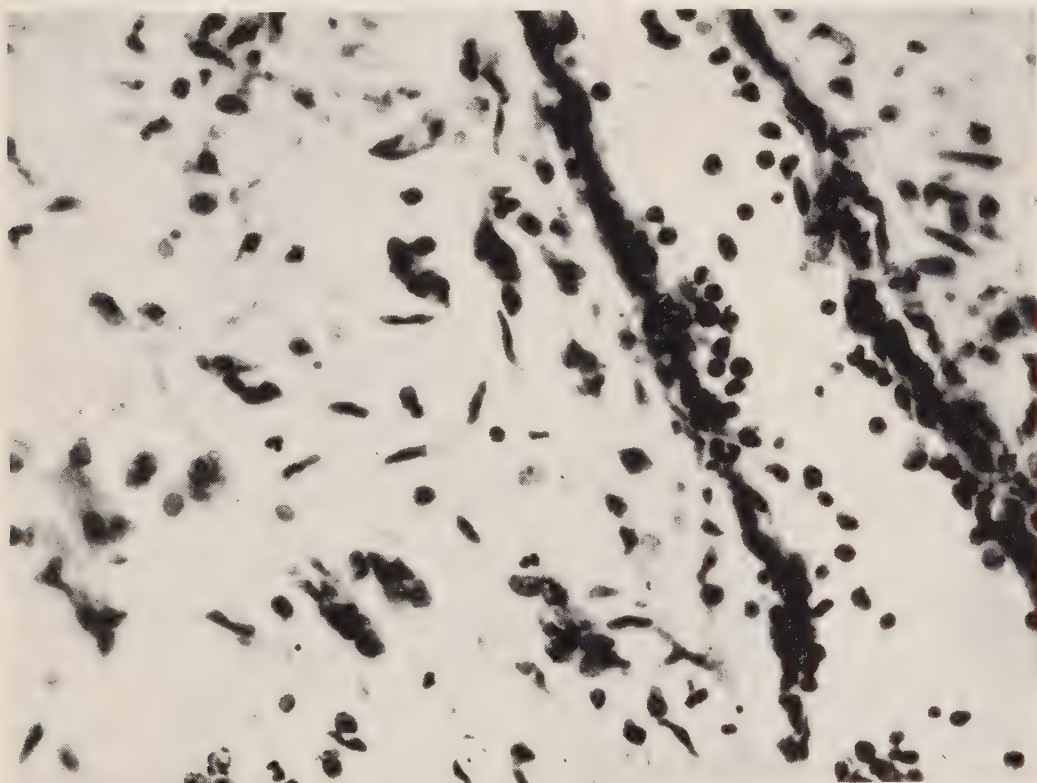
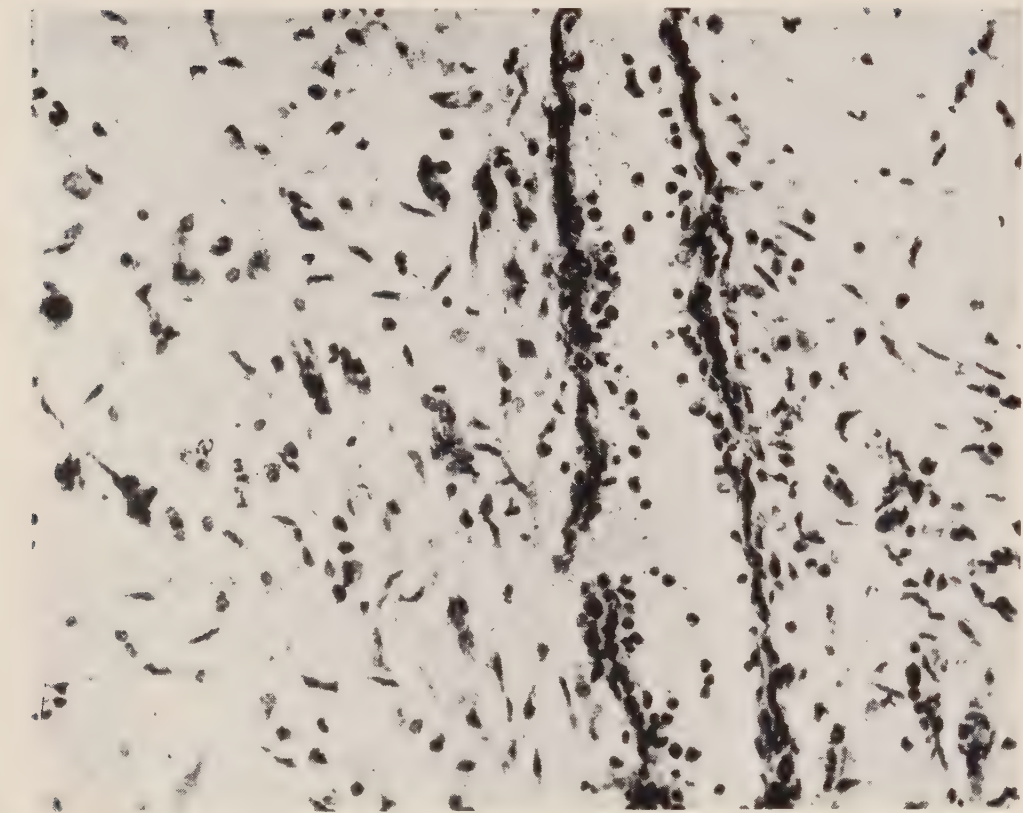


FIG. 5. *Spinal cord.* Early stage of microglial proliferation showing large number of rod-cells present. Nissl. (Hurst.)





PLATE IV  
EXPERIMENTAL POLIOMYELITIS

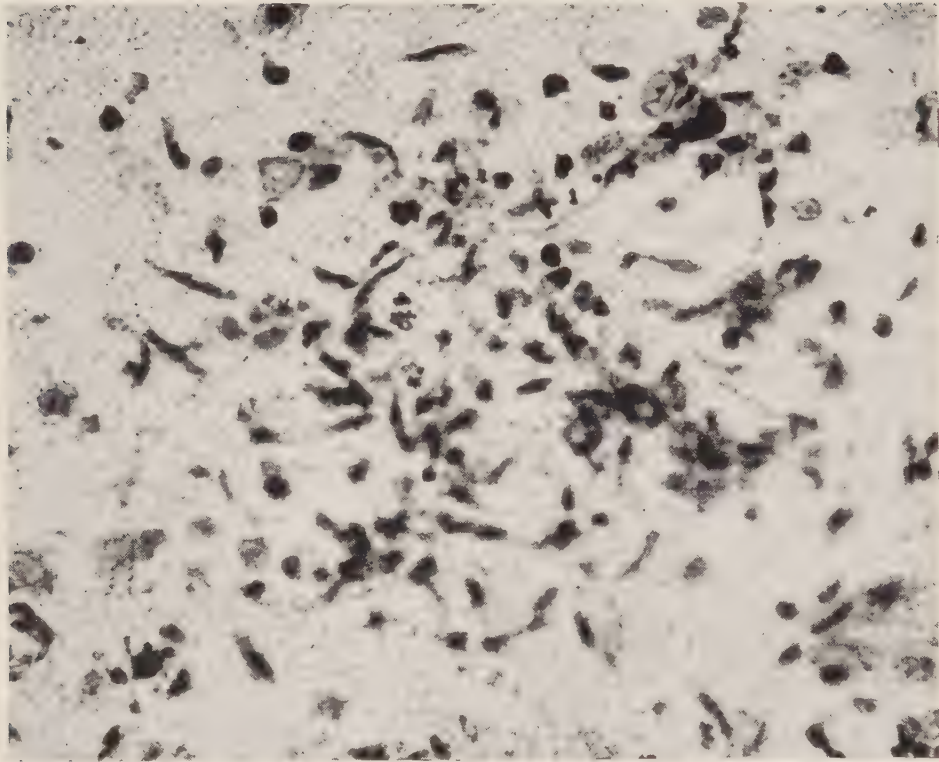


FIG. 6. *Spinal cord.* Focus of microglial proliferation in early stages of infection showing many rod-cells. Nissl. (Hurst.)

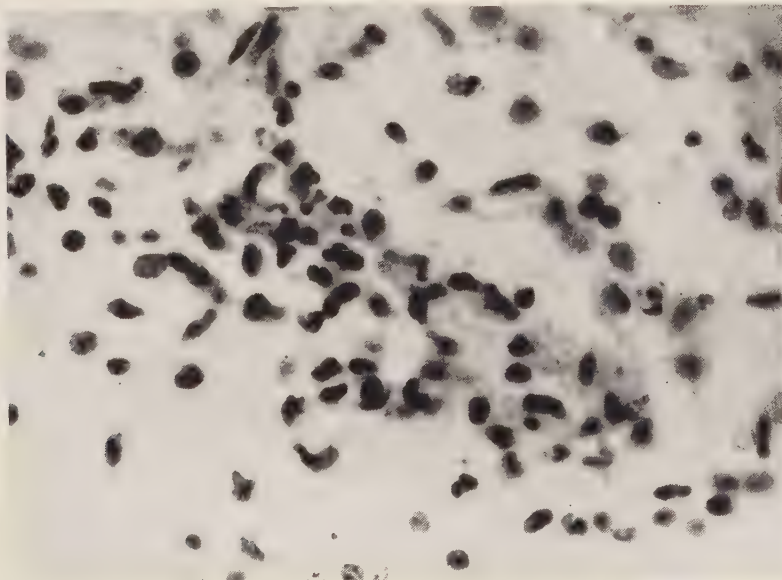


FIG. 7. *Spinal cord.* Focus of microglial cells, the so-called polyblasts, in the later stages. Nissl. (Hurst.)









PLATE V  
EXPERIMENTAL POLIOMYELITIS



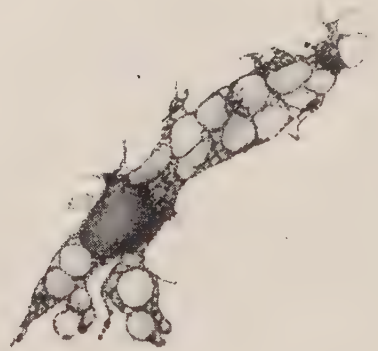
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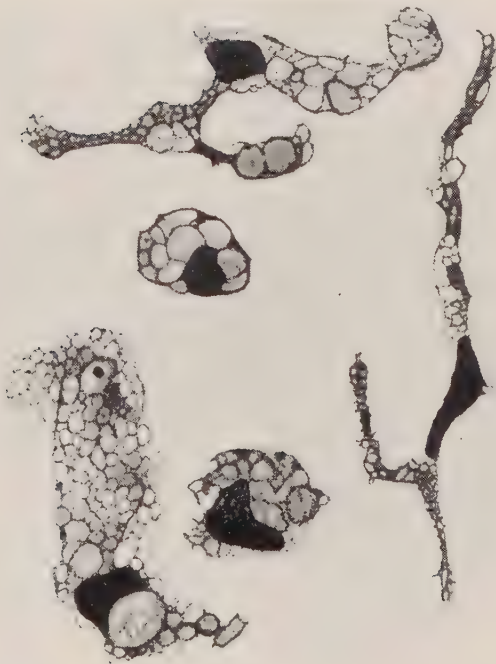
C



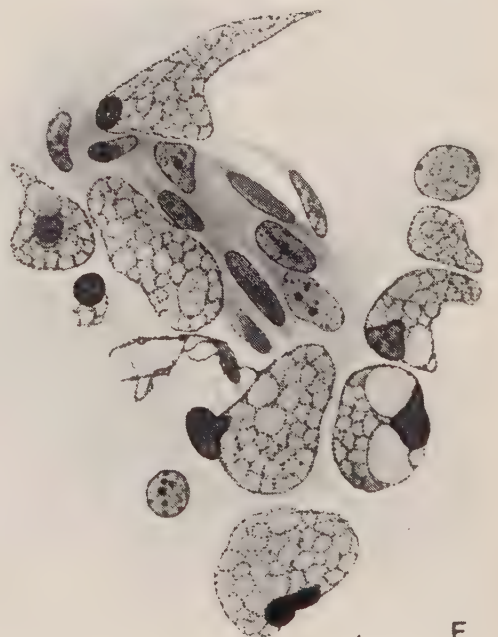
B



D



E



F

J. R. FORD  
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## EXPLANATION OF PLATE V

All the drawings in this and the next plate are to the same scale but *D* and *E* of Plate VI are from celloidin, while the remainder are from frozen sections.

*A-F*. Various stages in the evolution of the microglia.

*A*. Normal microglial cell.

*B*. Early alterations consisting in thickening and reticulation of the main processes with loss of many of the finer branchings. First day of paralysis.

*C*. Further retraction of the processes which contain numerous argentophil granulations. First day of paralysis.

*D*. Almost complete loss of the processes with vacuolation and reticulation of the cell-body. The vacuoles do not contain fat. Second day of paralysis.

*E*. Group of cells occupying the site of a vanished nerve-cell, the so-called polyblasts. The vacuoles do not contain fat. Third day of paralysis.

*F*. Typical granular corpuscles loaded with fatty globules; stage of reparation. *Penfield's method*. (Hurst.)



damaged nerve cells; some are grouped around the small vessels and capillaries, while others, even when followed through several sections, are apparently independent of either.

The number of polymorphs present varies according to the exact stage of the disease and the virulence of the virus inoculated; with the virulent Fl. strain they are at first extremely numerous and form a high percentage of the satellite cells of severely damaged neurons. Together with other infiltrating cells they tend in severe cases to overflow into the white matter adjoining the anterior horns, while a few may be scattered diffusely through the white matter or lie in the central canal. The rapidity with which they disappear is indeed striking and 48 hours after the first nervous symptom, usually very few are found.

Lymphocytes, like polymorphs, lie scattered through the tissues and take part in the focal infiltrations; they tend to be more numerous with the less virulent strains of virus and in the later stages of infection.

The microglia undergoes enormous proliferation and, except where polymorphs are very numerous, forms the bulk of the diffuse and focal exudate of the gray matter; a few small foci are sometimes seen in the white matter. By ordinary staining methods their appearance corresponds exactly to that of Wickman's "polyblasts." By the specific silver method of Del Rio Hortega or its modifications, however, the true nature of these cells is obvious and their progressive metamorphosis into granular corpuscles can be followed.

Changes in the neuroglia are usually not marked and these elements play a comparatively minor rôle in the infiltration.

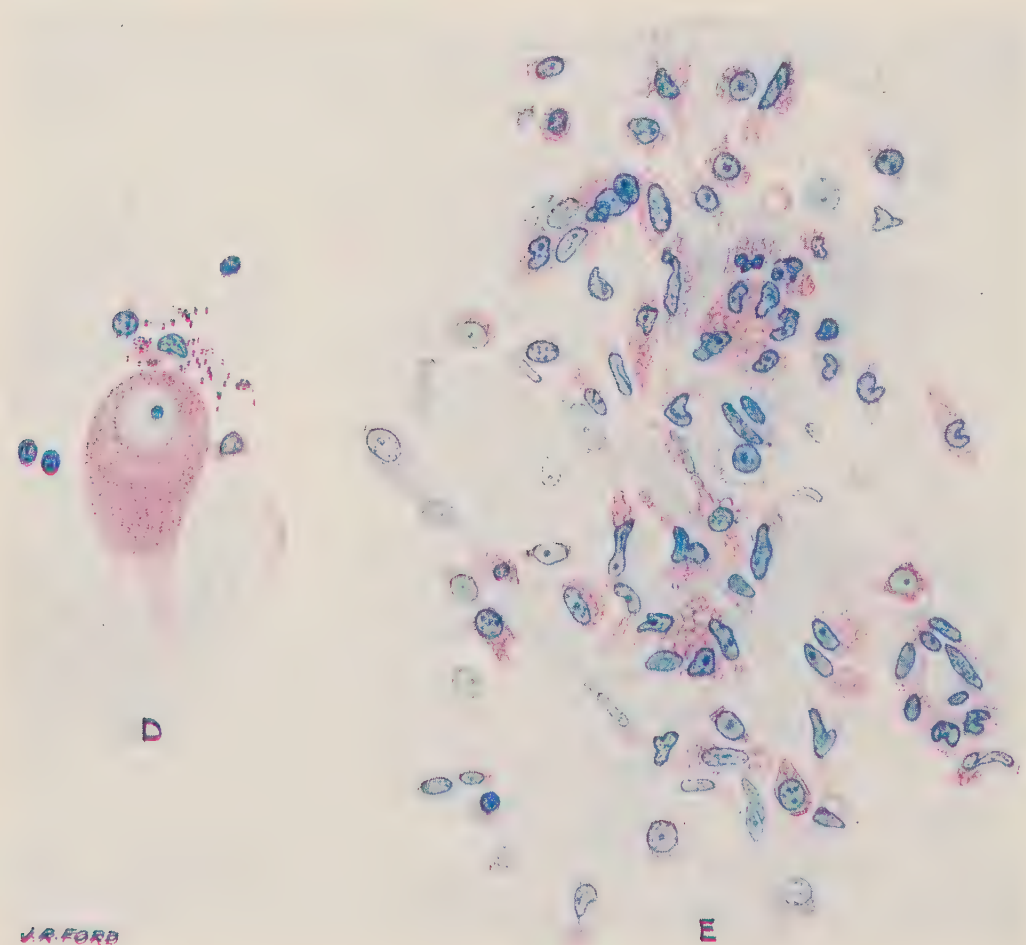
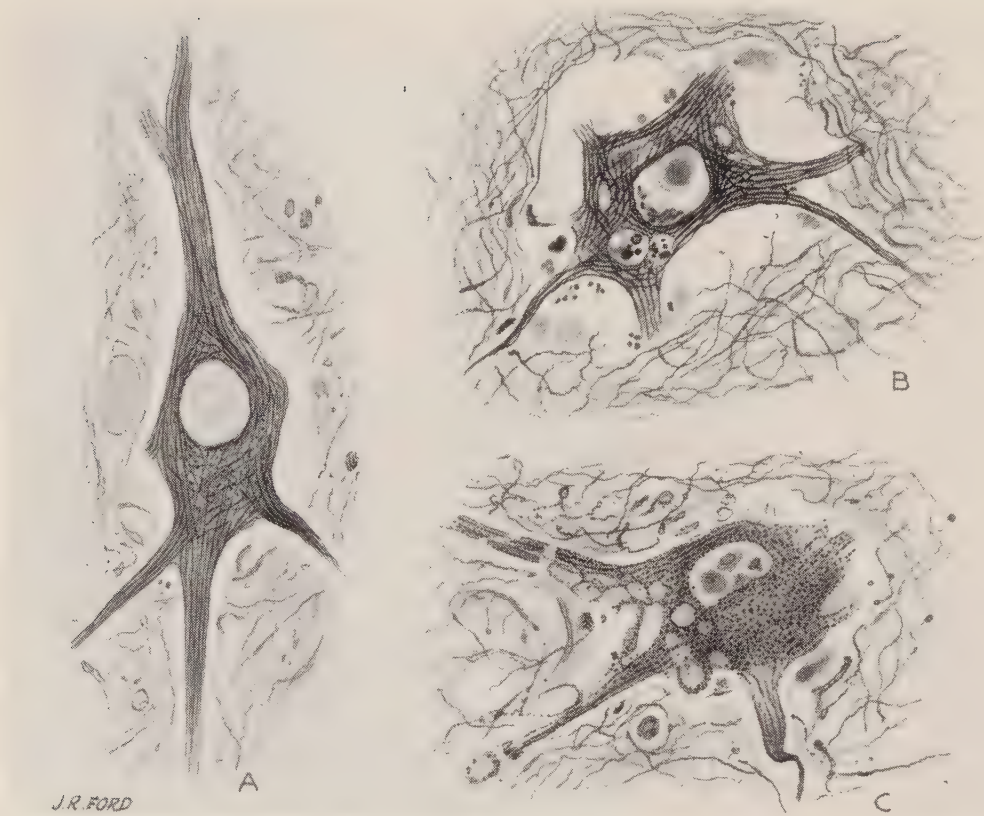
Whether other types of infiltrating cells are occasionally present or not is a very difficult problem, for it is no easy matter to determine the nature of every cell encountered in the nervous tissues. Cells identical in appearance with the mononuclear leucocytes of the blood are sometimes seen in the central canal and also in the perivascular exudate; presumably, between these two situations, they have wandered through the nervous substance where, however, they have never definitely been recognized. Plasma cells have never been seen.

(3) Nerve-cell destruction is at its maximum in the cervical and lumbar regions, where commonly from one-half to two-thirds of the anterior horn-cells are destroyed; sometimes, with the virulent Fl. strain almost all of them may be irreparably damaged. In the dorsal region many of the anterior horn-cells may suffer less severely, although even here a large number are destroyed outright. Death of neurons also occurs, though with much less frequency, at the bases of the poste-





PLATE VI  
EXPERIMENTAL POLYIOMYELITIS



## EXPLANATION OF PLATE VI

A-C. Stages in the destruction of neurofibrils.

A. Normal neurofibrillar network in large anterior horn cell.

B. Thickening of some neurofibrils; vacuoles enclosing polymorphs in the cell-body.

C. Granular disintegration of the neurofibrils with peripheral vacuolation of the cytoplasm.

*Bielschowsky method.*

D. Swelling and chromatolysis of nerve-cell; compare granules in the satellite microglial cell with the argentophil masses in Plate V, C.

E. Group of "polyblasts." Compare with Plate V, E.

Nissl stain. (Hurst.)



rior horns and especially in the cells of Clarke's column. The whole process is often extremely rapid. In the preparalytic stage when tremor alone is present only early lesions of the nerve cells are found; 24 hours later the majority of the anterior horn-cells may be necrotic masses of débris. After this first 24 hours there is a very sharp separation of the nerve cells into two groups; those which are obviously necrotic, and those in which the changes, mild or more severe, seem nevertheless definitely recoverable; it is rare to meet with cells which appear to bridge the gap between these two classes. Various types of neuron degeneration occur.

With the virulent Fl. strain acute necrosis is common. Cells so affected show at first little tendency to neuronophagia but later are surrounded by polymorphs lying in indentations of the margin of the cell, which they are obviously engaged in removing. A similar type of cellular destruction was noted by Craw (1931, C 31) in the parts of the cord most seriously attacked in a human case in which death had occurred 30 hours after onset.

With a less virulent infection the first change is central chromatolysis, followed later by complete chromatolysis. Both nucleus and cytoplasm may now swell and become very pale and the former disappears. More frequently, however, *the nucleus shrinks*, stains more darkly than usual and occupies an eccentric position in the cell; the abnormally large nucleolus may be extruded. The cytoplasm stains intensely in some parts, feebly in others; it becomes reticulated and then vacuoles appear, some of which reach a large size and contain polymorphonuclear leucocytes. In Bielschowsky preparations some of the neuro-fibrils stain more darkly than the remainder, while the intracellular network is distorted and opened up by a series of fine vacuoles; later there seems to be a comparatively small number of much thicker and darker fibrils, with a wider and more irregular meshwork than normal. Granular disintegration then sets in and all fibrillar arrangement is speedily lost.

As degeneration proceeds, neuronophagia begins. Polymorphs are rapidly replaced by microglial elements which soon assume the leading rôle and quickly remove the dead neuron.

Unaltered mitochondria were observed in nerve cells showing complete chromatolysis with considerable vacuolation; typical mitochondria could not be demonstrated in those undergoing neuronophagia, though numerous larger granules with similar staining properties but with no reaction for fat were seen and probably represented pathologically altered mitochondria.

PLATE VII  
EXPERIMENTAL POLIOMYELITIS

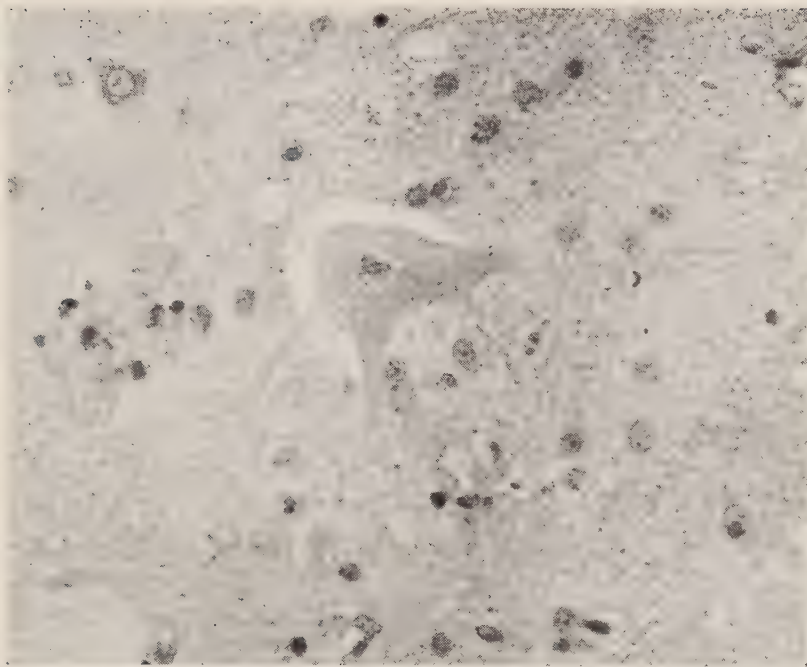


FIG. 8. *Spinal cord*. Necrotic ganglion-cell, scarcely distinguishable from ground substance. No phagocytosis. Infection with very virulent virus. Panchrom. (Hurst.)

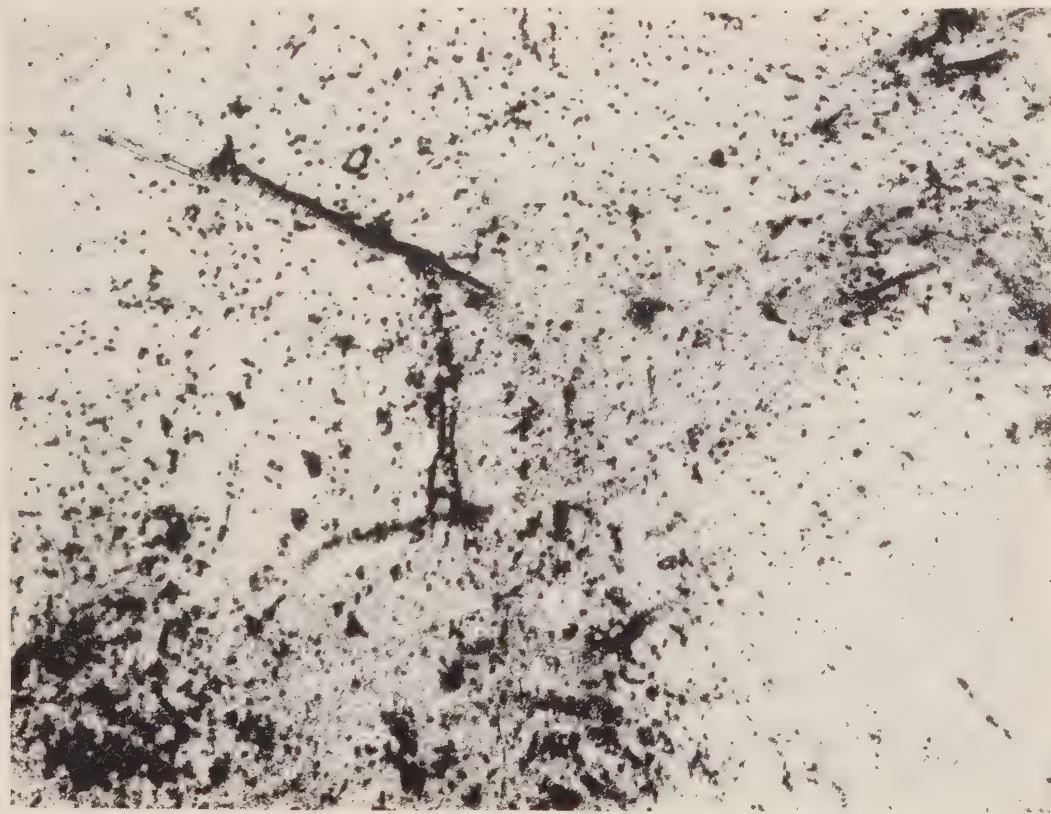


FIG. 9. *Spinal cord*. Perivascular, diffuse and focal infiltration with oxydase-positive cells. Gräff's method. (Hurst.)





PLATE VIII  
EXPERIMENTAL POLIOMYELITIS

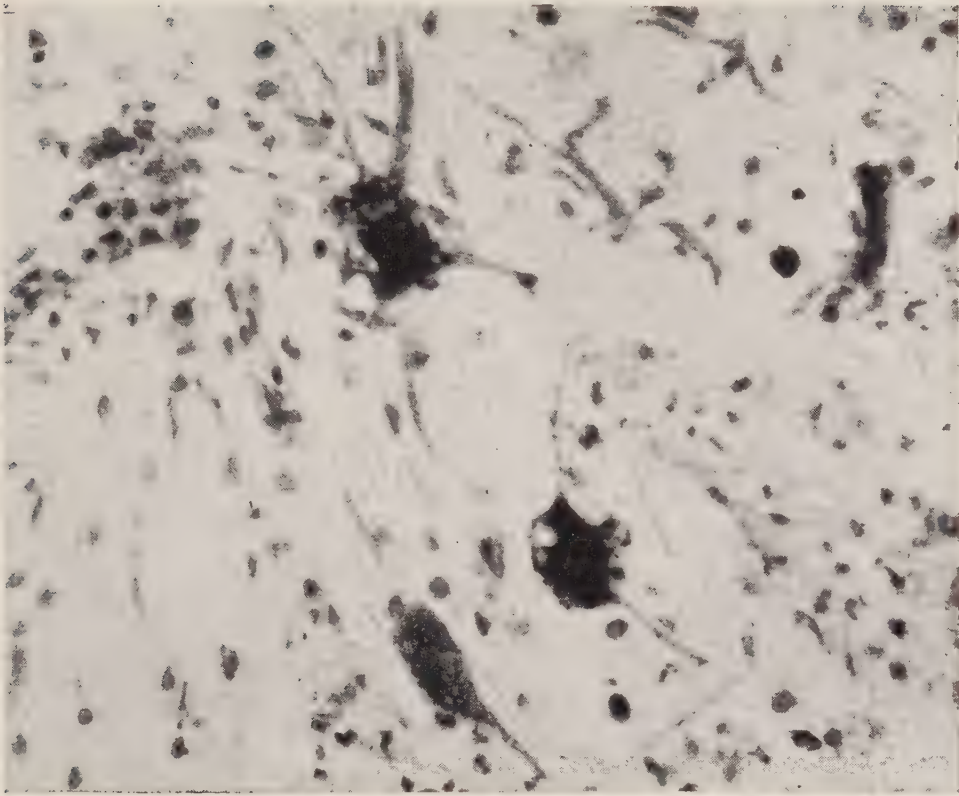


FIG. 10. *Spinal cord.* Vacuolar degeneration of nerve-cells. Above and to the left, a focus of neuronophages at the site of a vanished nerve cell. Nissl. (Hurst.)

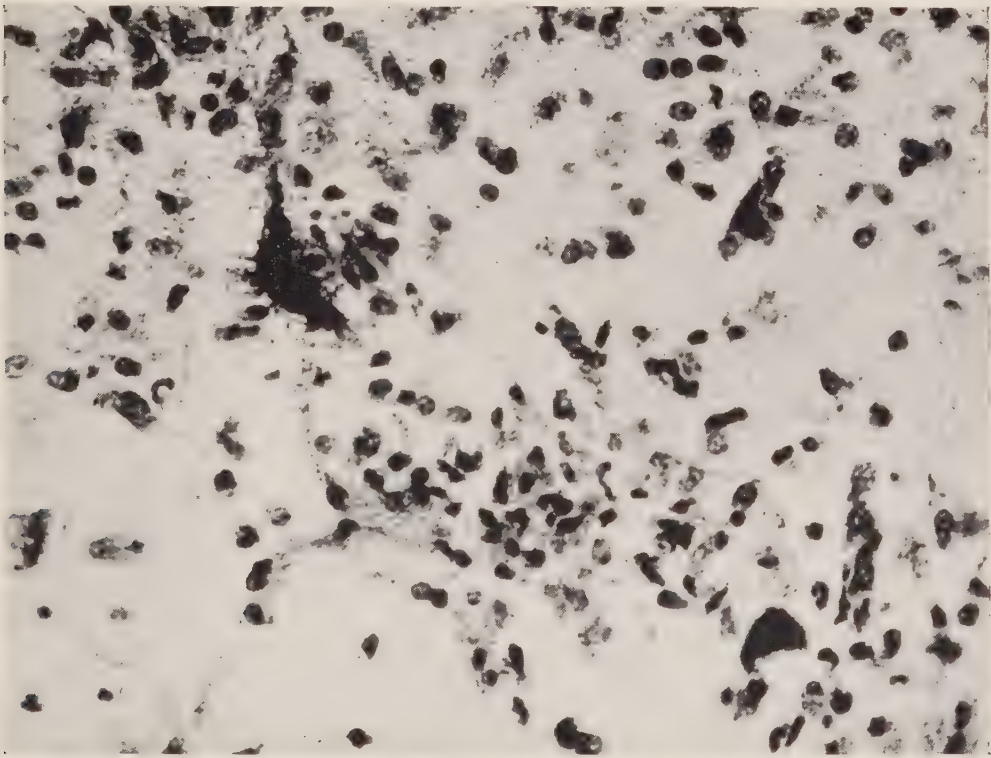


FIG. 11. *Spinal cord.* Vacuolar degeneration of nerve-cell. Focal accumulation composed largely of microglia ("polyblasts"). Nissl. (Hurst.)





PLATE IX  
EXPERIMENTAL POLIOMYELITIS

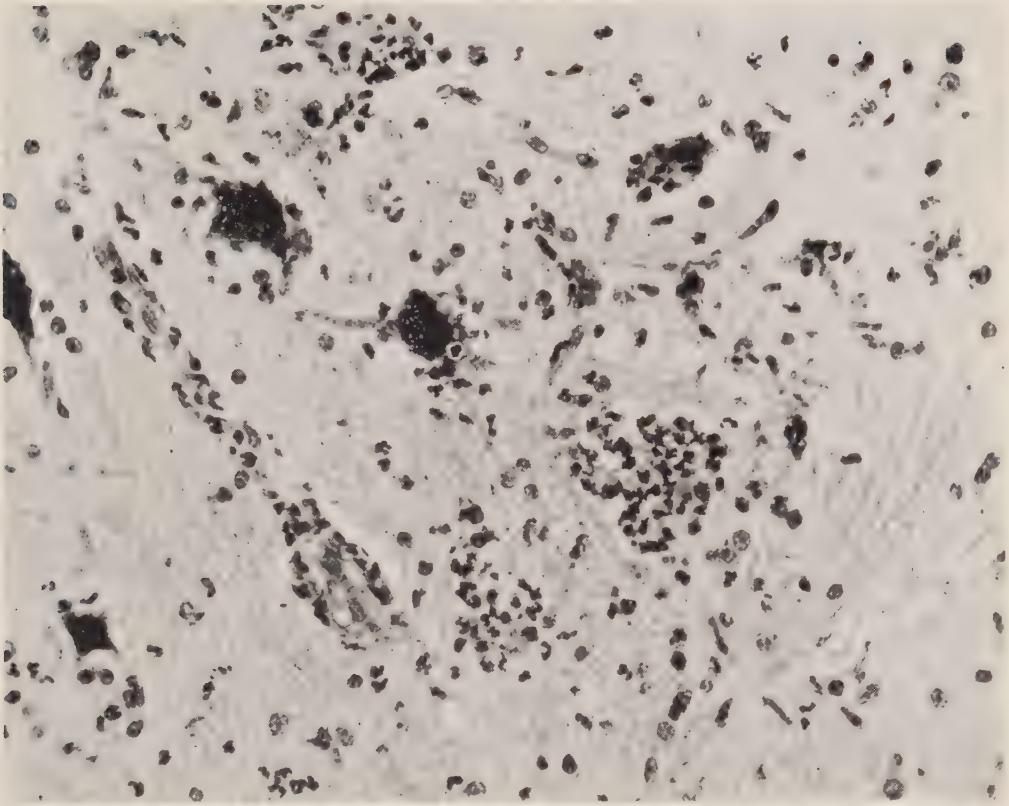


FIG. 12. *Spinal cord.* Lysis of nerve-cells by polymorphs. Iron-alum haematoxylin and eosin. (Hurst.)

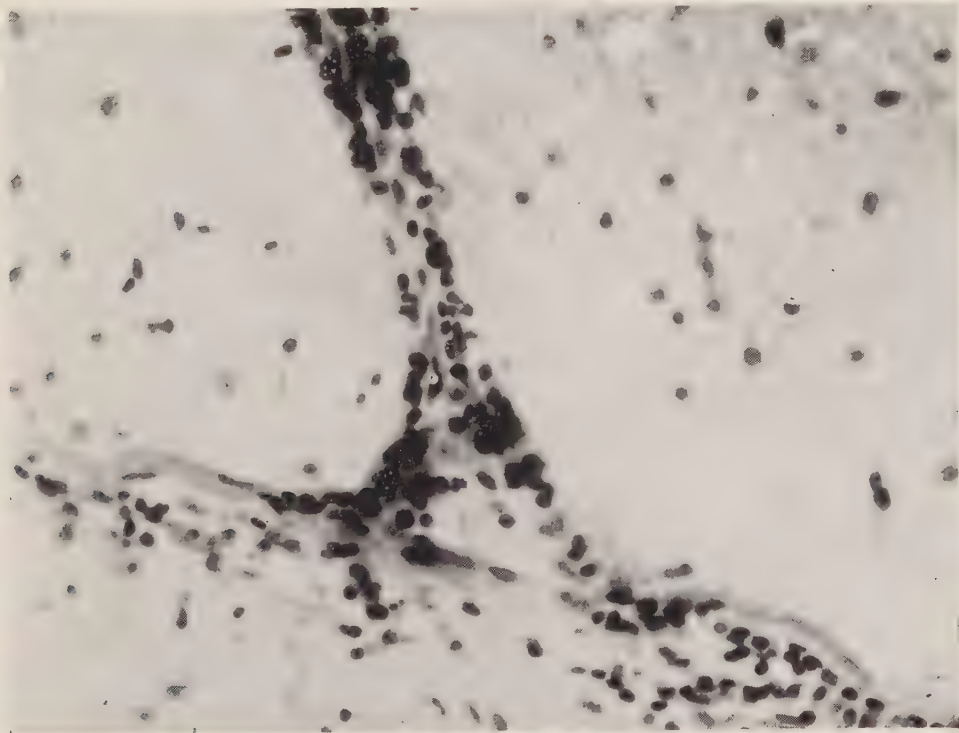


FIG. 13. *Spinal cord.* Passage of the cells of the perivascular infiltrate into the pial meshes. Iron-alum haematoxylin and van Gieson. (Hurst.)





The myelin sheaths corresponding to the damaged nerve cells become greatly ballooned in some parts of their course, but at this period actual fragmentation is not observed.

In 1 case the endothelium of many of the capillaries was swollen and some signs of early vascular budding were noted.

After having described the alterations in the spinal cord, Hurst gives a brief account of the lesions in other portions of the central nervous system and in other organs.

In the brain-stem similar changes are found. Perivascular infiltration in the floor of the fourth ventricle and in the substantia reticularis is frequently more intense than in the cord. Nerve-cell damage is never as severe as in the cord; occasionally a necrotic cell has been seen, but here, as in all the higher regions of the nervous system, complete chromatolysis with irregular staining of the cytoplasm and nuclear shrinkage and eccentricity are usually the most advanced lesions.

In the basal ganglia perivascular infiltration and small focal accumulations of microglia, polymorphs and lymphocytes are seen. Death of nerve cells was never observed.

In the cortex, foci of infiltration are scattered here and there in the gray matter, and perivascular infiltration is constantly present in both cerebral hemispheres. In most cases nerve-cell damage is mild in degree, and only in the motor cortex do some neurons succumb to the infection. A patchy meningitis is the rule and is more widespread than are areas of damage to the underlying cortex; it is most marked around the site of inoculation.

In the cerebellum similar lesions are present. The intervertebral and Gasserian ganglia suffer loss of some or many of their nerve cells, which undergo phagocytosis by the proliferated capsule cells; lymphocytes and polymorphonuclear leucocytes also take part in the formation of the pericellular foci. Foci of lymphocytes and perivascular infiltration also occur. Lymphocytic infiltration has been seen in the anterior and posterior nerve roots, and in a few cases in the sciatic nerves.

In other organs there were very few changes which were not present in the control monkeys. *Liver*: In about one-third of the cases round-cell infiltration of greater or lesser intensity was present in the portal tracts; 1 control was similarly affected. The infiltration did not correspond in degree with that in the alimentary canal. *Alimentary tract*: In all animals, both experimental and control, some degree of inflammation existed. The stomach, small intestine and large intestine all were involved; in a given case, any one of these viscera might show the most



marked changes, which consisted in round-cell, plasma-cell and sometimes eosinophil infiltration confined always to the mucous and sub-mucous coats. In 2 monkeys, some of the glands of the large intestine were dilated into small cysts. *Spleen*: This organ showed no appearances not also seen in controls. *Kidneys*: Only once was any abnormality—slight periglomerular fibrosis with interstitial and perivascular foci of lymphocytes—found in this organ. *Lungs*: A number of these animals were infected with ascari. One only of the present series of experimental animals suffered from tuberculosis affecting the lungs and bronchial glands. *Salivary glands*: In 3 cases round-cell foci were present in the submaxillary and parotid glands. *Muscles*: Several cases of sarcosporidiosis were found at autopsy. The *heart, pancreas, lymph glands, adrenals, thyroid, parathyroid, pituitary, testis and ovary* were never diseased.

One case illustrating the stage of recovery is described, that of a monkey killed 35 days after the first nervous symptoms. Throughout the whole length of the cord no meningeal infiltration or perivascular cuffing was evident, and at many levels the appearances were normal.

In the segments corresponding to the paralyzed extremities a striking diminution in the number of large motor neurons was observed. The surviving nerve cells at these and other levels were entirely normal.

In the same areas, microglial and neuroglial cells were definitely increased in number. The latter often took the form of large cells with a large pale nucleus and abundant protoplasm prolonged into numerous processes, but without definite fibrils. The microglial elements showed all stages in evolution from the normal to the typical, fully formed, fat-laden, granular corpuscles scattered through the tissues and accumulated in the neighborhood of the small vessels and capillaries; a few granular corpuscles were present in some of the perivascular spaces. Plasma cells or other indications of a persisting inflammation were wanting.

The myelin sheaths were reduced in number and many were ballooned at intervals or showed irregularities of staining. Globules and droplets of lipoid staining by the Weigert-Pal method lay free in the tissues of the anterior horns. Degeneration of the medullated fibers passing out into the anterior nerve roots was evident, but no tract degeneration was seen. Secondary changes were present in the corresponding peripheral nerves and muscles.

In the subsequent discussion these findings are compared with those of many earlier observers; the following are the main conclusions reached by Hurst.

PLATE X  
EXPERIMENTAL POLIOMYELITIS

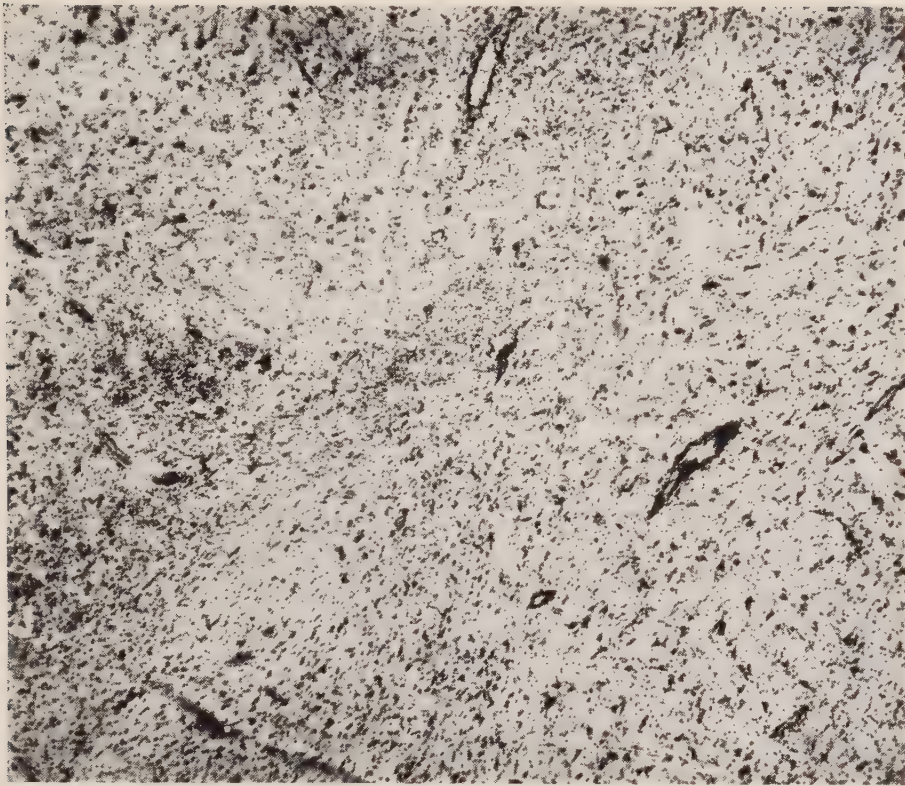


FIG. 14. *Pons*. Perivascular and diffuse tissue infiltration. Nissl. (Hurst.)



FIG. 15. *Cerebellum*. Focus of microglial cells and lymphocytes in white matter. Iron-alum and haematoxylin and van Gieson. (Hurst.)





PLATE XI  
EXPERIMENTAL POLIOMYELITIS

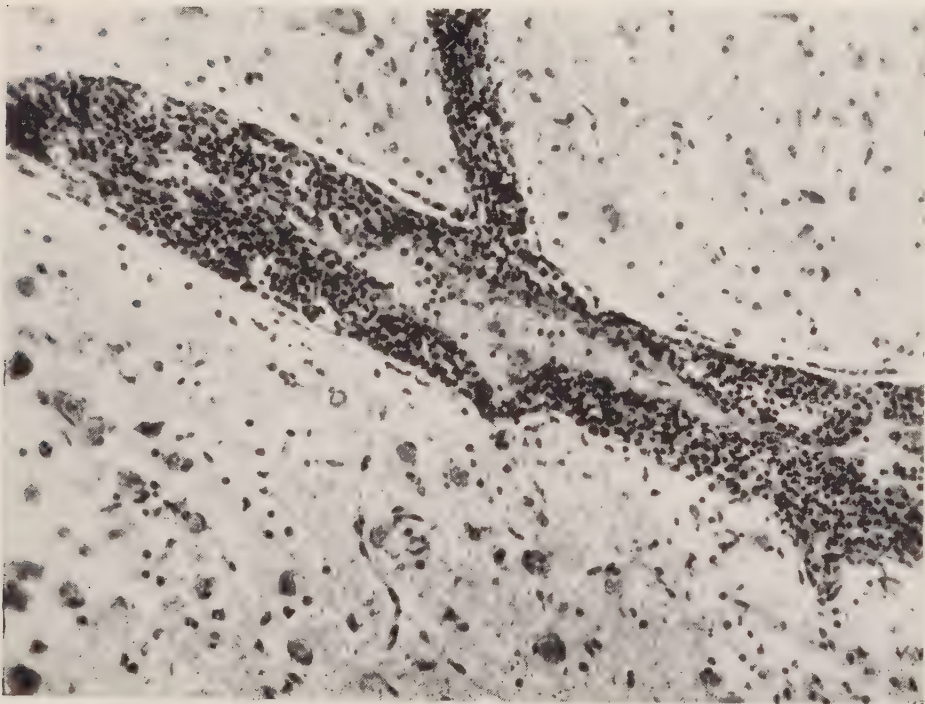


FIG. 16. *Mid-brain.* Perivascular infiltration. Iron-alum haematoxylin and van Gieson. (Hurst.)





PLATE XII  
EXPERIMENTAL POLIOMYELITIS

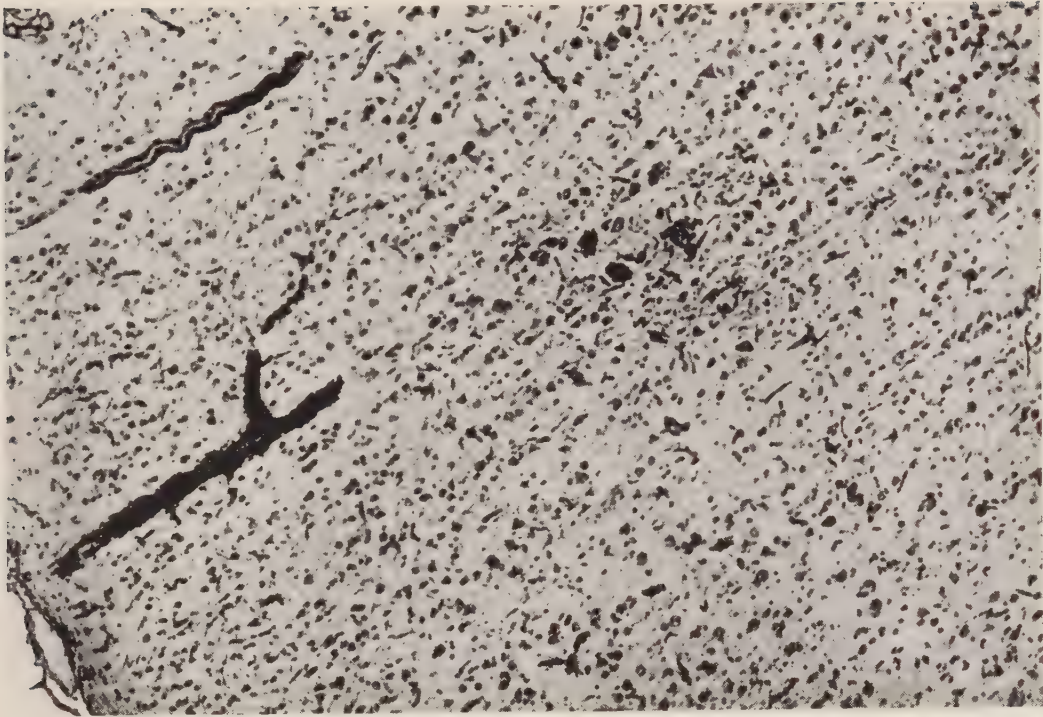


FIG. 17. *Cerebral cortex*. Perivascular infiltration. Several small foci of neuronophages corresponding to destroyed nerve-cells. Iron-alum haematoxylin and van Gieson. (Hurst.)



FIG. 18. *Spinal cord*. Stage of recovery; note absence of large neurons from the anterior horn on the left side of the photograph. Nissl. (Hurst.)





Poliomyelitis is a disease of the whole nervous system, including the intervertebral ganglia and peripheral nerves. Yet the brunt of the virus attack is borne by the anterior-horn cells of the spinal cord. None of the existing theories to account for this are adequate, and it can only be supposed that these cells manifest a special susceptibility to the action of the virus. Hurst (1931, H 42) has since observed a similar selective action of the virus of "loup-ill" on the Purkinje cells of the cerebellum. The nerve-cell degeneration is not mainly due to impaired nutrition resulting from the interstitial inflammation or from edema, but represents a direct attack of the virus on the functional nervous elements.

Allowing for the different periods of the disease at which various observers have obtained material for study, and for differences in nomenclature, no serious discrepancy was found in the various accounts of the types of cells present in the perivascular exudate. The probable origin of these cells is discussed.

The diffuse and focal tissue infiltrate is not definitely related to the vessels. The divergence of opinion regarding the nature and origin of its constituent cells has been considerable. Modern advances in technique permit us to recognize the "polyblasts" of Wickman, the "elongated glial cells" of McIntosh and Turnbull, (M 4), as microglial cells in process of transition to granular corpuscles. The oxydase reaction allows us to confirm the disputed occurrence of polymorphonuclear leucocytes; this phase is very transient but oxydase granules may perhaps for a time persist in the tissues after the breakdown of the enclosing cell. Lymphocytes also play a part in the cellular reaction.

Meningitis has usually been supposed to be the primary lesion of the disease. The above study suggests that it occurs only at a relatively late stage when the distended perivascular spaces of the interior of the cord are discharging their surplus cells into the meshes of the pia. The bearing of this observation on the spread of the virus is discussed in the next paper.

Hemorrhages, described by many writers as a prominent feature in acute poliomyelitis, are often due merely to injury to the greatly congested vessels as a result of trauma at autopsy.

Having presented a picture of the histopathology of the experimental disease, Fairbrother and Hurst (F 6) undertook an investigation of "the pathogenesis of and propagation of the virus in experimental poliomyelitis." A virus of almost constant incubation period (5 to 6 days) was employed. By passage of various parts of brain and cord at differ-



ent intervals after intracerebral, intranasal, and intrasciatic inoculation, and by full histological studies made at the same periods, the path of the virus was traced. At the same time the symptomatology in the affected monkeys was compared with that of the human disease.

When the first series of these experiments was performed, intrasciatic inoculation was unsuccessful, apparently because every effort was made to avoid trauma to the nerve fibers. Later, Hurst (H 40) found that if the nerve fibers were injured with the injecting needle, uniformly positive results were obtained.

The authors' argument with regard to the development of the paralyses may be given first. Statistics show that in the human disease paralysis most frequently affects one or both legs and that, even when the paralysis is more extensive, symptoms are first apparent in the lower extremities. The same order of development of paralysis has been noted in monkeys after intracerebral inoculation. In the present series of animals (3 of which were inoculated intranasally, and the others, almost without exception, into the left cerebral hemisphere), 70 per cent showed the first evidence of muscular weakness in the legs. When one leg alone was involved, it was "almost always the contralateral limb. This crossed paralysis strongly suggests that some decussating mechanism participates in the spreading of the infection. . . . Although histological examination has shown that at the time of onset of symptoms, lesions are present at all levels of the cord, paralysis is nearly always complete in the legs while power still remains in the arm-muscles. This earlier abrogation of function of the lumbar-cord cells is evidently not due to the fact that they are first involved by an ascending infection but to a special susceptibility to the action of the virus. . . . The frequency with which the legs are first involved after intracerebral inoculation into monkeys shows that the symptomatology in human cases cannot be accepted as evidence of entry of the virus by the intestinal tract."

The path of spread of virus from the left parieto-occipital region to different parts of the central nervous system appeared to be as follows. At the site of inoculation the virus, after maintaining the same degree of virulence for several days, tended to diminish in activity, and on occasion disappeared entirely. The cerebrospinal fluid took no demonstrable part in its transfer to the cord. Virus could be demonstrated in the homolateral and contralateral optic thalamus and in the pons before it appeared in the spinal cord; at this time no symptoms other than a high temperature were evident. Virus appeared simultaneously

in all parts of the spinal cord at a time coinciding with the first nervous manifestations of the disease. In the cerebral cortex virus was found only in the motor area, and there not regularly; it seemed that the cerebral cortex was not a favorable site for its development or preservation.

Intranasal inoculation of a single dose of virus was not uniformly successful in the hands of these investigators. However, the results in those instances in which the disease was established "indicate the possibility that the infection has travelled by the fibres of the olfactory nerve to the olfactory bulb and tract, and thence directly through the nervous substance to the spinal cord. . .

"After intrasciatic inoculation a very definite sequence in the infection of different regions of the central nervous system may be observed. That sequence runs as follows: lumbar cord, leg area of the motor cortex, cervical cord, arm area of the motor cortex. Further, the motor cortex corresponding to the inoculated nerve is infected before that of the opposite side; this suggestion that a decussating mechanism is involved in the transmission of the virus, already obtained from the symptomatological survey . . . is again received. Other regions of the cortex contained virus less often. The optic thalamus corresponding to the inoculated limb is infected early; in one experiment that of the opposite side did not show virus at a fairly late stage. The cerebrospinal fluid may or may not contain detectable amounts of virus; it is, apparently, not infected at an earlier stage than the spinal cord or motor cortex."

The histological findings are as follows:

**Intracerebral Inoculation.** On the first and second days thereafter "meningitis is widespread over the cerebral hemispheres, but only rarely, and over extremely small areas, is infiltration found in the brain-stem or cerebellum; the meninges of the cord are never affected. Changes in the nervous tissues are found only at the site of inoculation . . .

"By the third and fourth days, early lesions have appeared in the homolateral but not in the contralateral thalamus, in the cortex immediately adjacent to the inoculated area, and, in some cases, in the mid-brain and pons; the cord is normal. General meningeal infiltration has not spread to the brain-stem and inflammatory cells are present in the pia only where an infiltrated vessel of the deeper tissues reaches the surface.

"On the fifth day, that is the day or the day preceding that on which definite paresis is manifest, meningeal infiltration may or may not be marked over the cerebral hemispheres; its intensity and distribution



vary from case to case. With it is associated perivascular infiltration of the superficial parts or the vessels penetrating the cortex. Cellular foci and perivascular infiltration in the deeper cortical layers are much more frequent on the inoculated side and occur in the absence of overlying meningeal infiltration. More common near the vertex than at the base or on the lateral surface of the hemisphere, they are numerous around and in front of the site of inoculation, in an area including the parietal and posterior part of the frontal lobes, but rarely occur in the anterior part of the frontal and the occipital lobes. The cornu Ammonis seems always to be spared. Lesions in the putamen and caudate nucleus are insignificant but the homolateral globus pallidus, anterior perforated space and amygdaloid nucleus show much perivascular infiltration. The intense lesions in the homolateral thalamus and hypothalamic region are continuous with those in the mid-brain, which, in one case at least, was definitely more affected on the inoculated side. No definite chain of lesions through the white matter connects the inoculated area with the basal nuclei; only occasionally is perivascular infiltration seen in this situation and then in a vessel lying immediately beneath an affected part of the cortex. On the contralateral side, early lesions occur in the thalamus and hypothalamic regions especially in the regions nearest the mid-brain; cortical lesions are less numerous than but of similar distribution to those on the other side. Early lesions are present at many levels of the brain-stem and cord. Nerve-cell degeneration is already severe in some anterior-horn cells, even in the absence of local interstitial changes, but cellular foci are scattered at random over both anterior and posterior horns. Meningeal infiltration occurs only where an infiltrated vessel reaches the surface and is evidently due not to a primary meningitis but to an overflow of inflammatory cells from the distended perivascular spaces of the deeper vessels.

“By the eighth day, the fully-developed disease described is present. While the damage in the brain-stem, and particularly in the spinal cord, had increased greatly in severity to produce general paralysis and complete prostration, that in the cortex and basal ganglia is not very much more severe than on the fifth day.

**Intranasal Inoculation.** “Difficulty in obtaining infection by this route prevented [a demonstration of] the exact sequence of pathological changes, but several important points emerge.

“Although over the cerebrum of one animal meningeal infiltration was very intense and widespread, in the other it was scanty and less than is often seen after intracerebral injection. Near the vertex, cortical

lesions are of very similar distribution to those in the intracerebral group of experiments, though the area of their maximum incidence is rather further posteriorly. In addition, however, the basal cortex of the homolateral hemisphere, but not that of the other side, suffers severely. The amygdaloid nucleus shows cellular foci and perivascular infiltration and the cornu Ammonis, spared in the other group, is here affected. The homolateral thalamus and globus pallidus are relatively less involved; the putamen and caudate nucleus escape. Other lesions are similar to those outlined above.

"Thus while on the contralateral side the appearances are very like those seen after intracerebral inoculation, on the homolateral side lesions occur in both basal and vertical cortex and are relatively less severe in the basal nuclei."

**Intrasciatic Inoculation.** "In the inoculated sciatic nerve, the inflammatory reaction is of moderate degree and does not spread far above the damaged area. The upper part of the nerve remains microscopically normal and the first signs of poliomyelitis appear, at approximately the same time, in the lumbo-sacral cord and the spinal ganglia.

"In the lumbar cord at an early stage meningeal infiltration is often intense, but the vessels of the grey and white matter are at the same time heavily cuffed and it is impossible to decide whether the meningeal infiltration represents a primary meningitis or is a secondary phenomenon due to drainage of cells from the cord vessels. The experience with M-271, at the earliest stage examined, shows that definite lesions in the grey matter may occur in the absence of any meningeal change. Neuronal degeneration occurs very rapidly, and even in those animals killed at the very onset of muscular weakness a certain proportion of the anterior horn cells have already undergone complete necrosis. Lesions occur first on the inoculated side and, as far as the infiltrative changes are concerned, to an equal extent in the anterior and posterior horn; they then spread rapidly to the opposite half of the cord, where there is more tendency to a major affection of the anterior horn, and upwards to other levels. In the dorsal and cervical segments the side of the inoculated nerve suffers before the other, and the disease almost always begins in the anterior horns; here meningeal infiltration is definitely preceded by nerve-cell degeneration and inflammatory changes in the deeper tissues. While this spread to the dorsal and cervical cord takes place with considerable rapidity, extension to the motor cortex is usually still more rapid, so that virus and lesions appear here while the cervical cord is still unaffected. Similarly, early lesions may



be present in the medulla before the cervical cord is involved. Later, the typical picture of poliomyelitis is obtained at every level from the lumbar cord to the mid-brain.

"At higher levels meningeal infiltration is of variable intensity and occurs in patches, usually at the base or on the lower part of the lateral surface of the hemisphere. It is not associated with the deeper cortical lesions (deep cellular foci and perivascular infiltration), which, except in two animals, have been confined to the motor cortex. In one case a single cellular focus was found in the cortex of the island of Reil and in one (advanced) case a few foci were present in the post-Rolandic convolution. These cortical lesions develop first on the side representing the inoculated sciatic nerve and only later and in smaller numbers on the opposite side; in the same manner, though lesions here are never very numerous, the corresponding optic thalamus is infected before the other. The caudate nucleus and the putamen of the lenticular nucleus remain normal, but definite, and at an advanced stage severe lesions are found in the hypothalamic region, the tissues around the third ventricle and the globus pallidus."

In their discussion Fairbrother and Hurst present the argument for the theory of the pathogenesis of poliomyelitis which they have formulated: "The belief is prevalent that extension of the inflammation in poliomyelitis occurs by way of the meninges, that meningitis is the first lesion of the disease and that from the meninges the inflammatory process spreads along the vessels to the anterior horns of the spinal cord . . .

"When we consider the march of events as determined by histological examination during the incubation period and early stages of the disease, many facts emerge which cannot possibly be explained by the theory under discussion. After intracerebral inoculation into the parieto-occipital region, lesions appear first in the homolateral thalamus and then in the hypothalamic nuclei, the tissues around the third ventricle, and the mid-brain. The pons is next involved and almost immediately afterwards foci of inflammation appear simultaneously at many levels of the medulla and cord. Cellular foci are numerous in certain areas of the homolateral cortex. Meanwhile the infection is spreading upwards into the contralateral thalamus and cerebral cortex. After intranasal inoculation we have, for reasons explained, been unable to ascertain the exact order of development of the lesions, but meningitis is evidently not an essential feature, for one animal with marked lesions in the central nervous system showed a scanty meningeal infiltration of very restricted distribution.

“It must at once be admitted that certain appearances in the cerebral hemispheres cannot well be due to anything but a meningeal spread. Here, from the earliest stages, there is always more or less meningeal infiltration and this is closely related in its extent and distribution to the lesions described as superficial perivascular infiltration. The involvement of the globus pallidus, often restricted to infiltration of the perivascular sheaths, may be similarly associated with and apparently secondary to meningitis over the anterior perforated space. On the other hand, deep cortical foci and perivascular infiltration of the cortex are of entirely independent distribution. After intracerebral inoculation they are numerous only near the cortex, and mainly in the posterior part of the frontal and the parietal lobes; the area of their maximum occurrence is the same in both hemispheres. After intranasal inoculation a very similar distribution obtains with additional lesions at the base, in the frontal and temporal lobes. While, therefore, we cannot altogether exclude the participation of the meninges in disseminating the infection, especially to certain regions, we conclude that, considering the nervous system as a whole, other structures play a more important part.

“Various considerations suggest that the main route of transmission of the virus is the nerve-fibre. Inoculation at the site mentioned places the infective agent in a region intimately connected with the thalamus, where the first lesions subsequently appear. From here, the tissues around the third ventricle and the mid-brain, where at first there may be a marked preponderance of lesions on the inoculated side, are readily infected. From the thalamus and mid-brain a whole series of possible paths are open to the virus and it appears significant that at an early stage, when lesions in the cord are first evident, the foci are scattered at random over the whole grey matter, both sensory and motor. When weakness is manifest first in one leg, it is nearly always in the contralateral limb, showing that some decussating structure is involved. The mode of spread of the disease into the contralateral hemisphere forcibly suggests an extension from below. Only after intranasal inoculation and on the side inoculated do deep cortical foci occur with any frequency near the base, in areas intimately connected with the olfactory apparatus. In fact, with the reservations made in the preceding paragraph, no appearances have been encountered which could not be explained by a spread of the infection along the nerve-fibres.

“If the virus spreads by nerve-fibres it might be expected that the nerve-cells would be primarily affected, while the old theory that they



suffer in consequence of the interstitial inflammation would be more in keeping with a spread of infection along the vessels from the meninges. That the former supposition is the correct one has been shown by Hurst (1929), and Greenfield (1929) also holds a similar opinion; the present work fully confirms this belief and shows that, in the cord, the anterior-horn cells are already severely damaged when the interstitial lesions are in the very earliest stage of their development.

"It will have been noted from the histological account that only occasionally is perivascular infiltration seen in the white matter of the cerebral hemispheres; the earliest lesions are in the nucleus most intimately connected by fibre-tracts with the inoculated area; but, until these fibres reach their destination and lose their myelin sheaths, the virus seems to be insulated and prevented from evoking the characteristic inflammatory reaction in the surrounding tissues. Poliomyelitis might thus be described as a disease travelling by nerve-fibres but manifesting itself only in areas containing nerve cells, and must be placed in sharp contrast with post-vaccinal encephalitis, disseminated encephalomyelitis, etc., where the most marked lesions are in the white matter and result from a direct assault upon the myelin sheaths. Schröder proposes the use of the terms 'polioclastic' and 'myelinoclastic' to indicate this difference.

"Finally, a study of the literature on other diseases due to neurotropic viruses, herpes, encephalitis, rabies, etc., shows that the belief in transmission of the infective agent by the axis-cylinders is steadily growing, while, as far back as 1903, Meyer and Ransom showed that tetanus toxin was absorbed by the motor end-plates and passed along the nerve-fibre. . . .

"Not only does the assumption that the axon is the main route of transmission of the virus of poliomyelitis agree more completely with the histological findings in the central nervous system, but on it also the varying success following different routes of inoculation can be readily explained. Provided that a virulent virus is employed, intracerebral inoculation is invariably effective, for the organism is placed in direct contact with the susceptible axis cylinders. Intranasal inoculation is not nearly so certain in its results and the virus evidently has some difficulty in infecting a sufficient number of nerve-terminations to be transmitted in infecting doses to the central nervous system; were the main spread by perineural lymphatic channels communicating with the sub-arachnoid space, there would be no reason why submucous injection of a very virulent virus should fail, as it often does, to repro-

duce the disease. Intraneural injection . . . must depend on some amount of trauma to the axons themselves. . . . Intraperitoneal and subcutaneous inoculation will obviously give very inconstant results, a fact well recognized by every experimenter. . . .

“Coming now to the distribution of the virus in the central nervous system, we find that while it is readily demonstrable in the brain-stem and cord, the results of inoculating various areas of the cerebral cortex are very irregular and inconstant; its appearance in the cord coincides with the development therein of definite lesions and if present before this stage it is in undetectable amount. Now this distribution does not correspond absolutely with the distribution of histological changes but does correspond with the distribution of severe nerve-cell degeneration. Hurst has previously commented on the fact that, while lesions are widespread throughout the nervous system, the severer forms of nerve-cell change, leading to complete destruction of the affected neurons, occur chiefly in the anterior horns of the spinal cord; in our study of the symptomatology we have also shown that, although histologically the disease first affects the mid-brain and pons and spreads thence to the cord, clinically the legs are usually first affected, and are later completely paralysed at a time when muscular power is still present in the arms, neck, and face. No anatomical or mechanical factors will explain these observations and it can only be supposed that the anterior-horn cells, and particularly those of the lumbar cord, are, by some inherent difference in their constitution, peculiarly susceptible to the action of the virus, or that the anterior horns are regions particularly favorable for its growth. These alternatives are probably merely different aspects of the same fundamental fact, for there is a considerable amount of evidence (Boycott, 1928) to show that filterable viruses multiply only while exercising their specific pathogenic properties; the observed distribution of virus might thus be predicted from a histological study . . .

“In describing the distribution of deep cellular foci in the cortex, we have shown that they occur around the site of inoculation or, in the case of nasal infection, at the base of the frontal and temporal lobes and also, after both routes of inoculation and in both hemispheres, in a zone including the pre- and post-Rolandic convolutions. Now the latter area represents the parts of the cortex most intimately connected by the great afferent and efferent tracts with the mid-brain and brain-stem generally, and it is probably legitimate to conclude that infection of the cortex has taken place from these lower levels where the lesions are



well-marked and the virus-content high; any other hypothesis will not explain the constant symmetrical disposition of the foci in the cortex of the two hemispheres. Small amounts of virus must of course go to other parts of the cortex but since this is a region unfavorable to its activity, no lesions are produced here; only in those convolutions connected by a large number of fibres with the chief reservoir of virus is the latter poured in in sufficient concentration to overcome the local resistance to its activity."

After intrasciatic inoculation had been carried out, the discussion was continued as follows:

"Compared with the results of our previous investigation, the present observations are complicated by the fact that on three occasions virus has been found in the cerebrospinal fluid. Since it is generally recognized that intrathecal inoculation is effective in producing the disease, in the absence of evidence of any other mode of spread the implication of the cerebrospinal fluid might be taken as proved. These positive findings were, however, made in animals the victims of the declared disease and during the pre-symptomatic period endeavours to detect the virus in the fluid were not successful. It is possible that in these positive cases virus had reached the intrathecal space by passive infiltration along the perineural lymphatics in much the same manner as albuminous exudate reaches and gives rise to an increased protein content in the fluid of severe cases of polyneuritis (Greenfield and Carmichael, 1925). The histological examination showed that, at a very early stage, lesions in the central regions of the lumbar cord might be accompanied by no meningeal infiltration, and that in the dorsal and cervical cord parenchymatous lesions invariably preceded meningitis, which appeared only when the central vessels were heavily sheathed and obviously pouring inflammatory exudate into the pial meshes.

"Other evidence also is available to show that the axis-cylinders play the more important part in dissemination of the virus and determining the distribution of the pathological changes. The influence of trauma on the result of intrasciatic inoculation and the shorter incubation period with this route of infection are suggestive. More weighty evidence is afforded by the observation that, at an early stage, not only are lesions invariably more marked in the left half of the cord (after inoculation into the left sciatic nerve), but that the next region of the nervous system to be affected is the right motor cortex. This infection of the motor cortex, or rather of that part representing the inoculated leg, takes place before the cervical cord shows either virus

or lesions; involvement of the leg area of the left motor cortex corresponding to the side of the cord involved at a slightly later period, and of the arm area of the right motor cortex follows only after an appreciable interval. Similarly, the right optic thalamus is infected before the left. No theory of the pathogenesis of poliomyelitis in terms only of the cerebrospinal fluid can provide a reasonable explanation of these observations.

“Nevertheless, apart from the detection of the virus, there are indications that infection of the cerebrospinal fluid contributes to the final picture of fully-developed poliomyelitis. The lesions in the motor cortex, which appear certainly to be due to axonic transmission, are situated in the deeper cortical layers and are not usually accompanied by infiltration of the overlying pia-arachnoid. Of quite independent distribution is the patchy meningitis over the base and lateral surface of the hemispheres. Insignificant at an early stage but sometimes becoming marked when the disease is at its height, this meningitis can hardly be attributed to anything but an irritative agent carried by the cerebrospinal fluid. It is necessary, therefore, to allow that the fluid assumes a supplementary rôle in disseminating the infection, but it can hardly be claimed, as did earlier workers, that it is the sole agent.”

More recently Hurst (1932, H 43) has studied the mechanism of infection following intrathecal inoculation (usually into the cisterna magna but sometimes into the lumbar theca).

Preliminary experiments on the distribution of dyestuffs (India ink and trypan blue) were carried out. They showed that after intracisternal inoculation the dye passed up the ventricular system as far as the choroid plexuses of the lateral ventricles. On the surface of the brain, staining was intense on the inferior surface of the cerebellum, along the basilar artery and anterior cerebral arteries, and around the interpeduncular fossa, spreading thence by the Sylvian fissure and adjacent convolutions to the vertex and medial surface. The Rolandic fissure and the motor cortex were among the most faintly stained areas. Where staining was most marked dye had passed for considerable distances down the perivascular spaces, but none was recognized in the nervous tissues except (*a*) in very occasional microglial cells lying immediately below the pia, and (*b*) in the floor of the fourth ventricle where ink-laden polymorphs had carried particles for a considerable distance into the nervous substance.

The pieces of cortex chosen for passage included areas of both maximal and minimal staining. The distribution of virus was strikingly different from that of the maximum dye coloration.



In another experiment a loop of string was introduced beneath the dura, and, after time had been allowed for adhesions to form, virus was inoculated into the closed space bounded only by meninges. The results will be gathered from the following discussion.

"Infection by the intrathecal route occurred constantly and readily, without prolongation of the incubation period. The distribution of virus was comparable with that after other routes of inoculation; virus was frequently present in the motor area and only exceptionally in other parts of the cortex. In the cord the experimental and histological findings were usually in agreement, though in M-376 virus was present at a very early stage in the cervical cord, with a very long incubation in the passage animal, in the absence of lesions. Clark and Amoss (1914) found that after intraspinal injection the cerebrospinal fluid remained infective for two but not for six days; in the present investigation virus has been detected up to the fifth day.

"It was to be expected that the histological lesions also would show a distribution similar to that after intracerebral inoculation; to produce the disease, virus must invade the nervous tissues from the meningeal space and the conditions regulating its dissemination will then be those obtaining after direct inoculation into the brain-substance. The influence in this respect of axonic transmission was again evident in the close association existing between the lesions in different parts of the cord and in the motor cortex. In M-379, 470 and 377, either the cervical cord was more affected than the lumbar, or paralysis had begun in the arms, and foci were correspondingly numerous in the arm area; in M-451 and 450 the reverse was seen. The main difference apparent in the present group was the distinctly greater tendency towards the development of scanty lesions in parts of the cortex other than the motor area; this was, however, not sufficiently marked or constant to be of diagnostic value.

"Judging by analogy with the dye experiments, under the conditions of experiment virus regurgitated at operation into the whole ventricular system; potentially, therefore, invasion of the nervous tissue might occur at any one or numerous points over the whole meningeal and ependymal surfaces. Apart from the rather increased frequency of cellular foci in the general cortex, there was no histological evidence that virus had penetrated through the meninges covering the cerebral hemisphere. On the other hand, in three cases examined sufficiently soon after intracisternal inoculation, the only lesions present were in the vicinity of the fourth ventricle; this suggests that infection took place

through the ependymal lining of the ventricle. It will be remembered that in the India ink experiment this region alone showed definite penetration by the carbon particles. In the fourth early case (M-379) it was not possible to determine whether the lesions in the medulla had preceded those in the cervical cord. Though the difference between the distribution of virus in the cerebral cortex and that of the maximum meningitis or dye-staining (indicating the areas to which virus would have most ready access) was a striking one, we cannot without further proof assume an impermeability of the cerebral meninges, for in previous work it has been shown that the cerebral cortex is not a favorable site for growth or even for survival of the virus, though infection may follow its deposition here. Moreover, in two animals (M-472 and 451) inoculated by lumbar and by cisternal puncture respectively and examined at an early stage, lesions had evidently appeared first in the lumbar region, suggesting that virus may have passed through the meninges here. Although the attempt to solve the problem by inoculation into a small closed space lined only by meninges resulted merely in some lengthening of the incubation period, it is by no means certain that in the abnormal condition of the meninges resulting from the preliminary operation the result has any significance in indicating the permeability of the normal membranes.

"A feature of this series was the sudden death of three animals which on the previous day had exhibited no symptoms or only early weakness of the arms and legs; in each the unusual picture of necrosis of almost every nerve cell in the pons and medulla afforded an explanation of the fulminating clinical course of the malady. It does not seem probable that each of these animals was abnormally sensitive to the action of the virus; it is more likely that the particularly severe affection of the brain-stem was associated with a massive infection through the floor of the fourth ventricle.

"From a consideration of human poliomyelitis in the light of the present and of previous findings we can only suggest, without categorically asserting, the probable course of infection. After intracerebral and intraneural inoculation into monkeys the major importance of axonic transmission is clearly evident. With intrathecal inoculation, evidence is again obtained that the axis cylinders determine the dissemination of virus which has penetrated the nervous tissues. The fact that the distribution of lesions after infection by any of these routes is essentially the same is not, therefore, sufficient ground for introducing an unnecessary complication by assuming that after intracerebral or



intraneural inoculation virus first enters the cerebrospinal fluid and is absorbed later into the nervous tissues. But in man direct evidence of the first step in infection of the nervous structures is wanting. It is extremely probable that invasion takes place from the nose or throat. The experimental work shows that it is quite possible for the virus to be transmitted to susceptible regions of the brain and cord without the intervention of the cerebrospinal fluid. It also shows, however, that poliomyelitis follows equally readily infection of the fluid, which could occur by way of the perineural lymph spaces of the cranial nerves, and that in most cases it is not possible from histological appearances in the fully developed case to determine with certainty the route by which virus has gained entry. An exception to this last statement possibly exists in infection through the olfactory nerve (Fairbrother and Hurst, 1930); a detailed examination of exceptionally favorable early human cases might lead to a decision on this point; Goodpasture (1925) believed that in his case infection had travelled up the glossopharyngeal and vagus nerves. The relative chances in favor of utilisation of these alternative paths are difficult to estimate, and possibly in different cases either may be used. In monkey poliomyelitis, however, several observers have shown that nasal inoculation is followed by appearance of virus in the olfactory bulb; Flexner and Clark (1912-13) found that two days after lightly swabbing the nasal mucosa with virulent material virus was present in the olfactory lobes but not in the medulla or spinal cord. These observations are easily explained if the axons are the transmitting agency, while there is no particular reason why virus passing up the perineural lymphatics into the cerebrospinal fluid should localise in the olfactory bulbs. It is difficult to see why after the virus had reached these nervous structures Flexner and Amoss (1914) found it necessary to assume a distribution by the cerebrospinal fluid, since this assumption introduced the unnecessary complication referred to above. Finally, although the present work shows that virus may still be present in the cerebrospinal fluid at least five days after inoculation, there remains the fact that virus has never yet been demonstrated in human fluid; examination of a sufficient number of cases at an early stage of the disease would, if negative, go far to show that the axonic route is the path of choice in man as in the monkey. Without evidence to the contrary there seems no reason to believe that the mode of production of poliomyelitis in man is dissimilar from that in the experimental animal."

Additional evidence of the spread of the virus along the axis cylinders

of the nerve fibers of the cord has been furnished by recent experiments described by Jungeblut and Spring (1930, J 28). The spinal cord of a monkey was transected at the level of the first lumbar vertebra. The severed ends were in free communication with the spinal fluid. On the seventh day following intracerebral inoculation, the monkey developed typical symptoms of poliomyelitis. On the ninth day the animal was killed and the two sections of cord removed. The cervical and thoracic cord showed typical histological lesions while the lumbar cord appeared normal. Inoculation of another monkey with the cervical cord resulted in the development of typical poliomyelitis but inoculation with the lumbar cord gave negative results. These authors subscribe to the theory of axonic spread of the virus in the central nervous system advanced by Fairbrother and Hurst.

Brodie (1932, B 31) has stated that he is in accord with the view of Fairbrother and Hurst that the disease process begins in the cord rather than in the meninges, and has given the following evidence in support of this hypothesis:

“(1) The cells in the sub-arachnoid space are usually deposited about the blood vessels and are of the same type as those in the perivascular spaces of the cord, so that it appears that the source of the cells in the meninges is from the perivascular spaces of blood vessels rather than from inflammation of the pia arachnoid.

“(2) In confirmation of the results of other workers, monkeys were not infected with large quantities of cerebro-spinal fluid removed from patients in the pre-paralytic stage, but it must be observed that this is not very strong evidence.

“(3) Two animals which were completely paralysed showed no pleocytosis during the course of the disease and the histological sections of the cord at the height of paralysis showed the usual changes in the grey matter, but the meninges contained no cells, whereas it is usual to find the cell count of the cerebro-spinal fluid increases from the onset of symptoms to the height of paralysis.

“(4) Inasmuch as the cerebro-spinal fluid of only two out of nine preparalytic and early paralytic human cases showed any increase in total protein, and since occasionally experimental animals, with a cerebro-spinal fluid count as high as 600 or 700 cells, showed no increase in globulin until the second day of paralysis, it is not likely that an inflammatory process was occurring in the meninges at this stage of the disease. An inflammatory process in the meninges would result in an early increase of proteins. It seems likely that the cellular



exudate is a response to the injury to the neuron rather than to inflammation of the meninges."

On certain points, however, Brodie's observations are not in complete agreement with those of the English pathologists. In his experience, after intracerebral inoculation, "there has been no marked evidence of a crossed paralysis for out of seventy-one monkeys, whose initial paralysis was observed, the paralyzes in forty were not localized to either side, in eleven on the inoculated side and in only twenty did paralysis occur on the uninoculated side." Moreover, "the arachnoiditis and perivascular infiltration, which occur in the brain after intracerebral inoculation of virus, may be solely due to reaction of cerebral trauma, such as was described by Nissl (N 30) and Devaux (D 11); and recently Hurst himself reported that after intracerebral inoculation of normal brain tissue, the pathological changes were similar to those occurring after the inoculation of virus emulsion. Only in one monkey, which developed a cerebral form of poliomyelitis, were specific lesions of poliomyelitis found in the brain and, in that case, the disease process was ascending in character. Therefore, any pathological changes that can be traced through the brain from the site of inoculation, are more likely to be nonspecific resulting from trauma rather than due to a spread of the virus."

Although Fairbrother and Hurst "believe that the virus spreads through the brain during the incubation period of the disease and that it has usually left the brain when paralysis has occurred," Brodie has found "that virus is present in many areas of the brain (pre- and post-Rolandic cortex, parietal cortex, basal ganglia, cerebellum, etc.) at the height of paralysis" and was also able to demonstrate virus in the cerebral cortex two days after the height of paralysis.

In the *Chapter on Etiology*, the distribution of the virus in the central nervous system and the rate at which it disappears after the height of paralysis have been described. Brodie (B 31; personal communication) has demonstrated a relation between the degree of infectivity of the nervous tissue and the character of the pathological changes. "By correlating the histological changes in the cerebrospinal axis with the distribution of the virus, at the acute stage of the disease, the infectivity of the virus appears to be directly proportional to the amount of neurophagia."

Histological examination of the central nervous systems of a series of 35 monkeys (intracerebral or extracerebral inoculation) showed that "the pathological changes in the grey matter were very irregularly distributed with decided quantitative differences in the amount of nerve destruction."

In the cord (Fig. 19), not only was the inflammatory reaction severe but the majority of the neurons were either partially or completely destroyed. In the medulla (Fig. 20), there was much less nerve destruction, although infiltration of the gray matter and perivascular exudate were almost as conspicuous as in the cord. The pons showed still less nerve destruction but almost as intense an inflammation as the medulla. At the level of the mid-brain, only an occasional neuron was affected, and in the cerebral cortex (Fig. 21), "specific nerve changes were rarely present . . . although interstitial and perivascular infiltration were often present.

"The infectivity corresponded more closely then to the amount of nerve destruction than to any other pathological change. The infectivity appears to be proportional to the number of destroyed nerve cells and so it appears that virus is localized in these neurones . . .

"The direct relationship between the infectivity and the number of destroyed neurones in a given area strongly suggests that virus is present in these neurones, as Levaditi and Pignot (L 49b) had previously proposed. Nerve cell destruction may very well be the result of the direct action of the virus in the neurones, as others have also supposed.

"Virus probably exerts its action and becomes fixed in the nerve cells very early in the course of the disease, for the author observed neuronophagia during the first stage of paralysis while Levaditi and Landsteiner (L 8) have reported it in the pre-paralytic stage of the experimental disease. Since phagocytic cells enter neurones only after their death or injury, the virus must exert its action even earlier in the disease than is evident by neuronophagocytosis . . .

"The cortex about the site of inoculation had less infectivity than the corresponding area of the uninoculated side, for which the following two explanations are offered. In the first place, traumatized tissue may not facilitate the growth of virus as well as intact tissue. In the second place, the infiltration of leucocytes and later of microglia that follows intracerebral inoculation, may destroy some of the virus . . .

"After the height of paralysis has been reached, the infectivity of the virus diminishes and co-incident with this, the pathological picture shows removal of neurones by phagocytes." In a section taken 2 days after the height of paralysis (Fig. 22), it may be seen that "many neurones have disappeared without any indication of outline except where several phagocytes fill the spaces. Perivascular collars and diffuse infiltration of polymorphs, mononuclears and rod cells are present."

Not infrequently, both in the human and in the experimental disease,



the paralysis does not attain its height at once but extension occurs over a varying period of time. It has not been definitely decided whether such an extension is due to edema or to a spread of the virus. In sections taken at various levels, however, Brodie has demonstrated types of cells, which represent different stages of the disease. This would suggest, therefore, that the extension of the paralysis is a result of the spread of the virus and not of edema.

It will be seen from the preceding that, although the pathological anatomy of poliomyelitis has received intensive study for a period extending over more than a hundred years, investigators have not yet reached an agreement with regard to the atrium of infection or the path of transmission of the virus within the organism. It is to be hoped that research will be continued along these lines until sufficient evidence has been obtained to permit an authoritative statement. In this chapter the opposing views on these debated questions have been presented as fully as possible; this has made it necessary to subordinate the description of the histopathology of the disease to a discussion of these subjects; additional details and excellent illustrations of both human and experimental poliomyelitis may be found in the references cited in the text.

### ANATOMICAL BASIS FOR OBSERVED CLINICAL TYPES

A discussion of the clinical types observed in the human and in the experimental disease is included in the *Chapters on Symptomatology and Etiology*. The pathology of the usual forms with lower motor neuron involvement has already been covered in this chapter. Brief mention may be made, however, of two of the less common types in regard to which some controversy has arisen, the cerebral or encephalitic, and the ataxic types. The character of the lesions that are found in the cerebrum and in the cerebellum has been described; they are usually less severe than those in the cord; and are less marked in the human than in the experimental disease, which is so often induced by intracerebral inoculation. It has been stated (Smith, S 48) that "in animal inoculation, there is almost regularly an encephalomyelitis and involvement of the cerebellum in 80-90 per cent of the cases. In man, on the other hand, as evidenced by these cases (from the 1931 epidemic in New York) less than ten per cent of the cortical and cerebellar sections show evidence of recognizable histologic changes." From an examination of human cases from the New York epidemic of 1916, Abramson

PLATE XIII  
EXPERIMENTAL POLIOMYELITIS

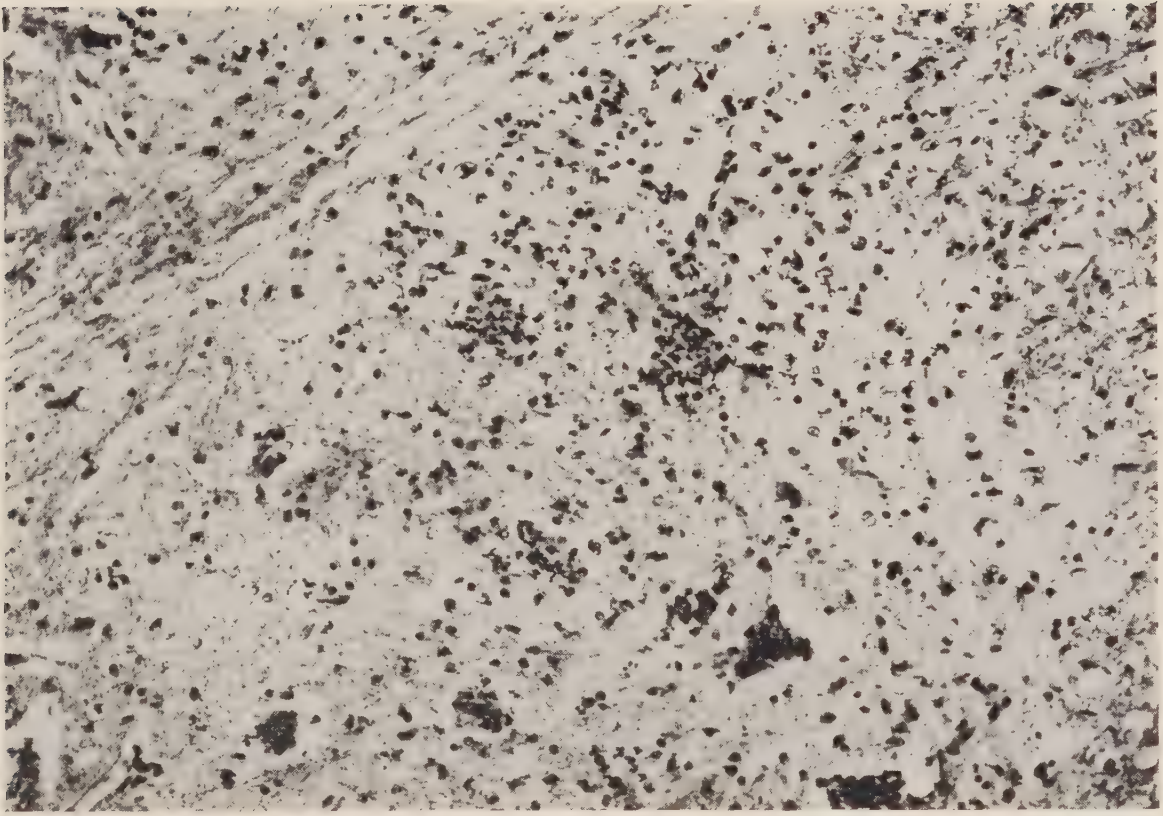


FIG. 19. *Spinal cord.* Extensive neurophagocytosis, diffuse infiltration of the gray matter. Weigert's iron-haematoxylin. Objective 16 mm.; projecting ocular No. 6; Bellow extension 115 cm. (Brodie.)





PLATE XIV  
EXPERIMENTAL POLIOMYELITIS

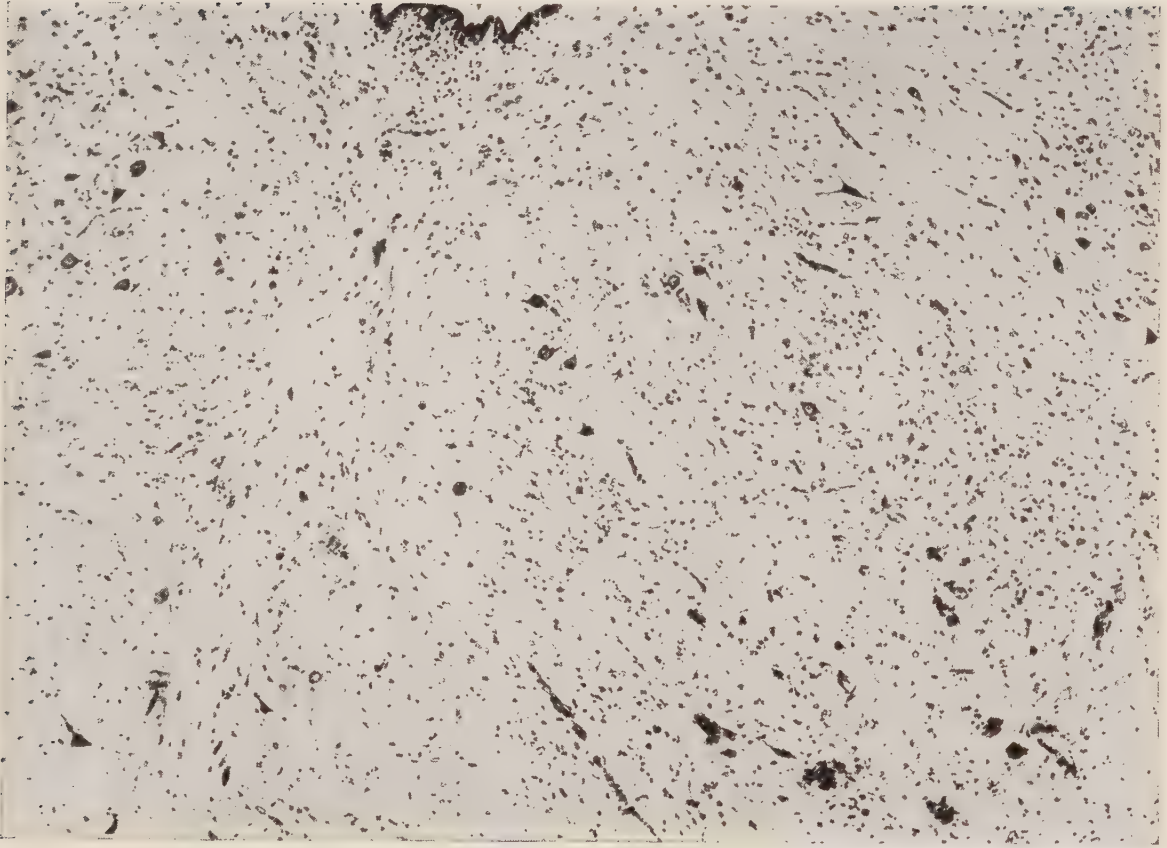


FIG. 20. *Medulla* through the IV ventricle. Neuronophagia of a small group of neurons (lower right hand corner) in hypoglossal nucleus. Others show chromatinolysis and pyknotic changes. Many appear normal. Weigert's iron-haematoxylin. Objective 16 mm.; no ocular; Bellow extension 115 cm. (Brodie.)





PLATE XV  
EXPERIMENTAL POLIOMYELITIS

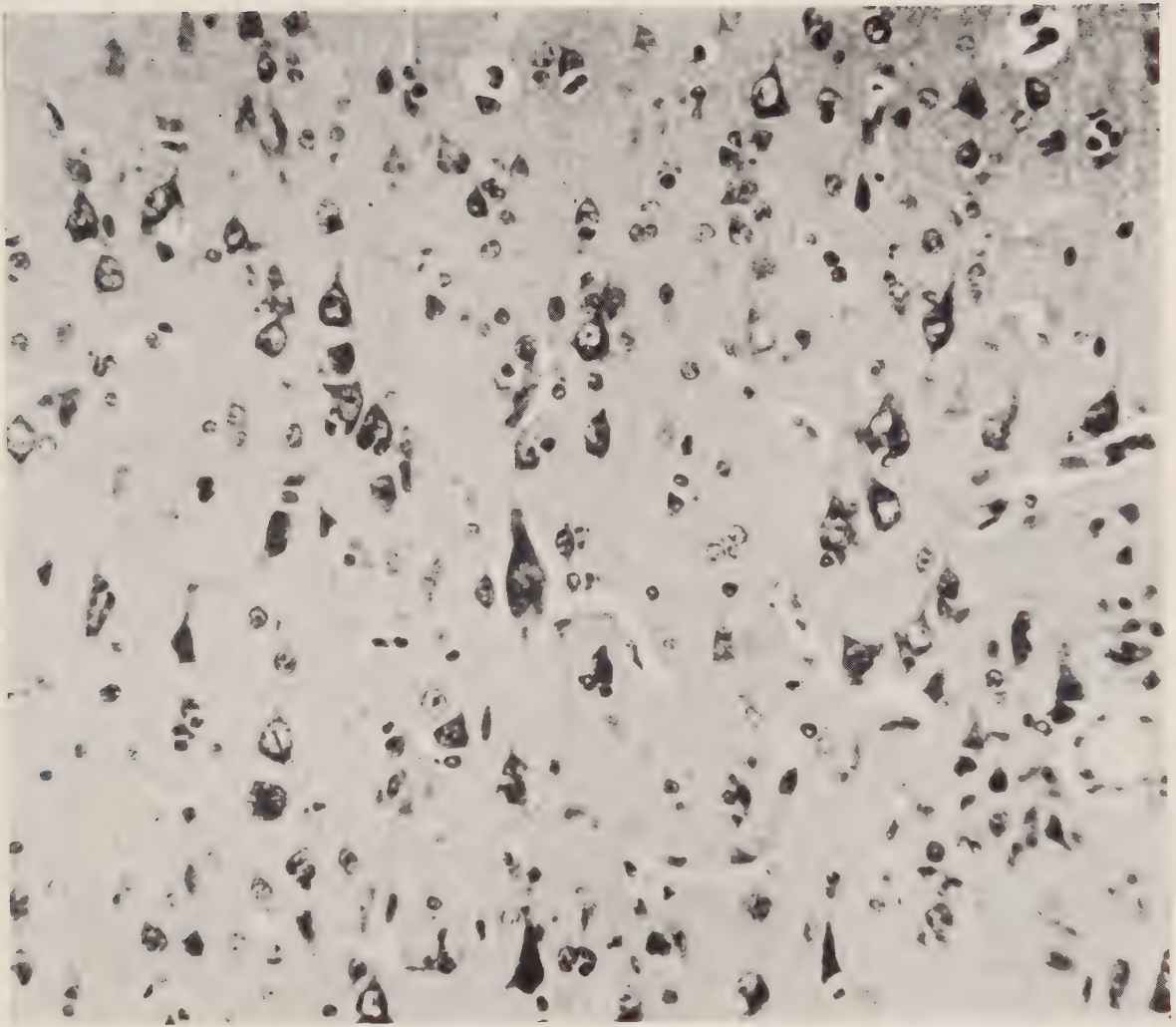


FIG. 21. *Motor cortex*. A few neurons show chromatolysis, otherwise the structure of the nerve-cells is normal. Weigert's iron-haematoxylin. Objective 16 mm.; ocular Homal No. 4, F 20 mm.; Bellow extension 52 cm. (Brodie.)





PLATE XVI  
EXPERIMENTAL POLIOMYELITIS

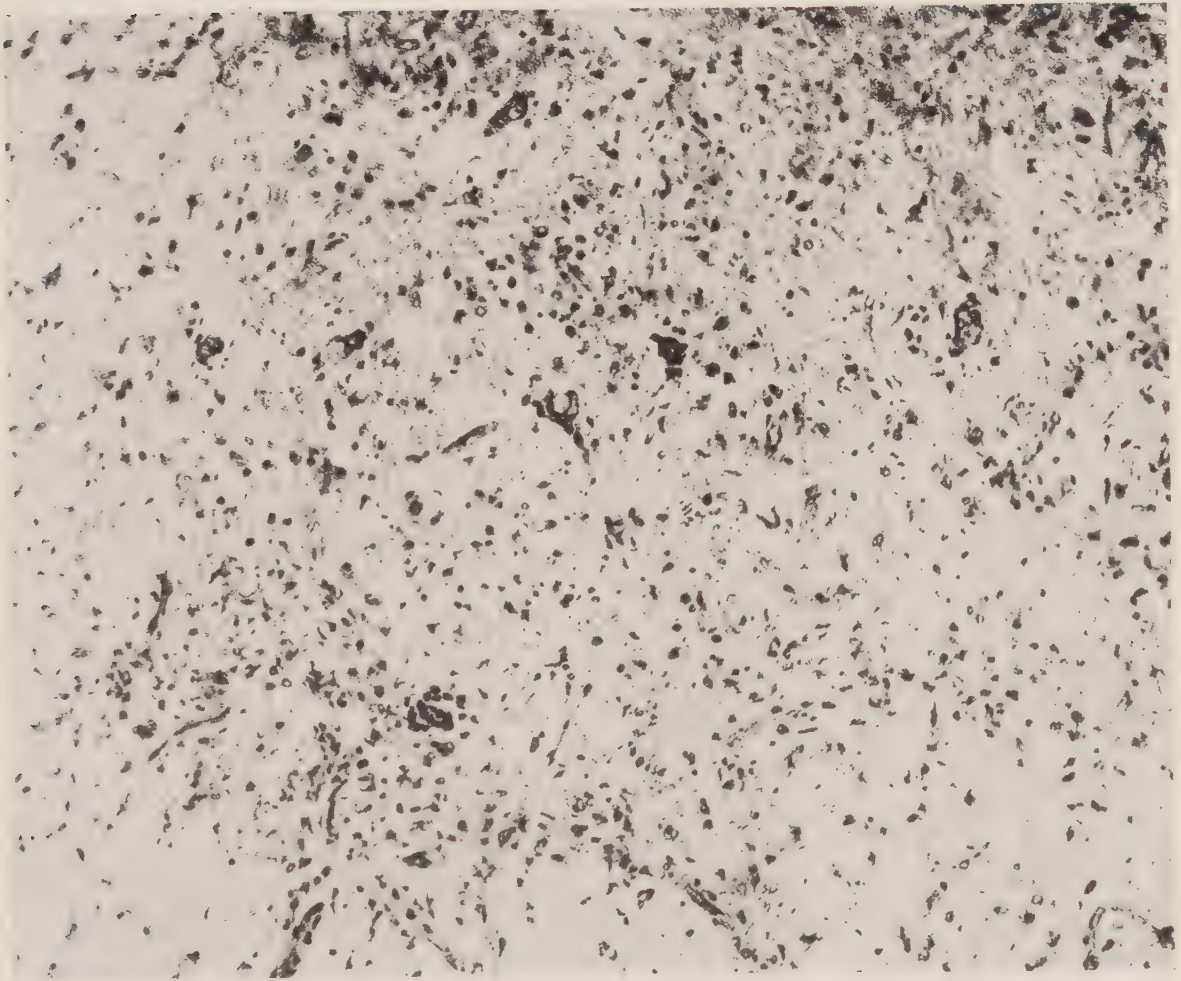


FIG. 22. *Spinal cord*, two days after the height of the paralysis. Many nerve cells have disappeared, leaving spaces which are partially filled with debris and phagocytic cells. Other neurons are disintegrating. Haematoxylineosin. Objective 16 mm.; projection ocular No. 6; Bellow extension 65 cm. (Brodie.)





(1918, A 4) noted very mild cell reactions in the brain in 14 of 37 cases; there was a mild degree of perivascular infiltration and, in a few instances, a focal accumulation of cells; but there were no degenerative changes in the nerve cells. Similar lesions occurred in the cerebellum in 5 of 33 cases examined.

The question arises as to the possibility of a specific pathology to account for the clinical findings in the forms under consideration. As the subject is reviewed completely in the *Chapter on Symptomatology*, it may be sufficient to state here that the clinical diagnosis of polio-encephalitis has rarely been supported by undoubted histological lesions; pathological evidence has, however, been afforded in a case of experimental poliomyelitis described by Brodie (personal communication to Dr. Neal). The meninges showed marked hyperemia; the exudate was largely polymorphonuclear in character and perivascular in distribution. In the white matter, an occasional collar of perivascular infiltration was found near the cortex. The gray matter was hyperemic, with a polymorphonuclear perivascular infiltration; there were focal areas of interstitial infiltration, which also consisted almost entirely of polymorphonuclear cells. There was edema, chromatolysis, and satellitosis of the neurons and neuronophagia of an occasional neuron in the motor cortex.

Many observers have commented on the fact that Clarke's column is frequently affected and that the intervertebral ganglia show histological alterations analogous to those found in the cord. As pathological changes in these locations as well as lesions in the cerebellum may result in lack of coördination, ataxia, and analogous manifestations, Neal and Abramson (1917, N 3) concluded that involvement of these areas provided the anatomic basis for the clinical signs observed in patients with the ataxic type of the disease. The literature on ataxic cases has been discussed by Howe (1919, H 32) together with a summary of the reported pathological changes in the cerebellum. He has concluded that "it would appear that the virus of anterior poliomyelitis does not have the peculiar affinity for the nerve elements of the cerebellum which it shows for the motor cells in the cord, and that the symptoms referable to the cerebellum are produced by interference with the function of its connecting nerve tracts and not by the destruction of its inherent nerve elements."



## STUDIES FROM THE 1931 EPIDEMIC

No attempt will be made here to give a complete report of pathological studies made in New York or elsewhere during the 1931 epidemic. Much of this material is still unavailable; moreover, it is not probable that any important discoveries will be disclosed.

As relatively little emphasis has been placed in the preceding paragraphs on the anatomical changes outside the central nervous system, it may be well to describe them more fully now. The recognition of alterations in locations other than the cerebrospinal axis is not new as has been pointed out earlier in the chapter. Recently, however, interest in such evidence of a systemic invasion has been revived. A description of extraneural lesions is included in Smith's report (S 48) based on a study of complete autopsy material from 81 fatal cases from the Willard Parker Hospital, and of incomplete material from an additional 53 cases from two other New York hospitals. The following is quoted from the sections describing the changes in the lymphoid structures and the visceral changes:

**"Lymphoid Tissue.** The reticuloendothelial system of the lymphoid tissue including the tonsils, thymus, spleen, retroperitoneal, mesenteric and cervical lymph nodes as well as the solitary lymph follicles and Peyer's patches of the lower intestinal tract are almost regularly and uniformly involved in an acute inflammatory process. This is evidenced by increase in size of these structures with marked congestion as a nearly regularly accompanying feature. The most striking lesions, as already noted, are seen in the Peyer's patches of the ileum where they may attain a size and degree of ulceration equal to that noted in mild forms of typhoid fever. Such lesions are well illustrated by Burrows in his recent article. In some instances, the inflammatory process has progressed to a point where actual necrosis can be made out with the naked eye . . .

"The microscopic findings in these structures are characterized first by oedema and congestion, often with associated hemorrhage. There is a rather diffuse lymphoid hyperplasia which is often marked enough to obscure the sinusoidal architecture of the organ. In addition, there is diffuse hyperplasia of the reticuloendothelium of the stroma occasionally with the formation of curious large atypical cells not unlike the cells one finds in Hodgkin's disease. The most noteworthy lesions of the pathology of the lymphoid system is seen in the follicles. The germinal centers, as a rule, are increased in size and stand out sharply

by reason of their relative pale staining. This is due to proliferation of the large cells of the germinal center. Not infrequently, one can find evidence of mitosis in these areas but the most striking feature is the degeneration, often going on to actual necrosis. In these cases, the follicle is made up of necrotic cellular detritus taking the eosin stain quite intensely. The changes in the spleen and tonsils are similar to those noted in the gastrointestinal lymphoid tissue and mesenteric lymph nodes but as a rule less marked in degree. The thymus shows a variable picture. Histologically, it is characterized usually by diffuse small round cell hyperplasia, by marked oedema and by no definitely uniform involvement of the Hassall's corpuscles. These vary greatly in number and in size as they do in the normal gland and our impression is that the reaction is essentially confined to the small cell element.

**“Visceral Changes.** In the stomach, we have noted a very high incidence of submucous hemorrhage associated with intense congestion of the mucosa. It has occurred in nearly seventy-five per cent of the cases, which seems to be too frequent to be entirely coincidental or negligible. This is usually superficial in nature but proceeds at times to a surface erosion of the mucosa. It is most marked in the fundus of the stomach, as a rule on the greater curvature. Its significance is not apparent but is in line with the theory of vascular endothelial damage by direct action of the virus.

“The lungs present a very variable picture. This is perhaps to be expected and is largely dependent upon the nerves involved. In those cases associated with respiratory paralysis, the characteristic feature is one of tremendous congestion posteriorly with a resultant emphysema anteriorly. In cases which have been in the respirator for any length of time, this relative emphysema may present an extensive process with loss of elastic tissue fibres in the alveolar walls.

“In the parenchymatous organs, especially the liver, kidneys and adrenals, there is usually demonstrated a moderate amount of granular degeneration of the sort usually described as cloudy swelling. This is frequently accompanied by rather marked congestion of the viscera but no specific pathology has been described. We have been unable to confirm the observation of certain other investigators who have observed the presence of focal lesions in experimental poliomyelitis in the monkey and in no case have we been able to observe any renal damage of a degree capable of producing symptoms or evidence of diminished renal function.”

We are indebted to Dr. Lewis Stevenson for the following account



of significant histological findings in the central nervous system of fatal cases from the same epidemic and for the photomicrographs illustrating his description:

"These observations on the pathology of the nervous system are based on the study of six cases of anterior poliomyelitis, five of them acute and one subacute. They are all from the epidemic of 1931 in New York City and came to autopsy in Bellevue Hospital.

"Four of the cases had received serum during their illness so that their pathology is not that of anterior poliomyelitis alone but is complicated by the effect of the serum on the nervous system and especially on the meninges.

"One thing is common to all of the cases, namely, the failure of the microglia cells to stain except in the form of compound granular corpuscles. This phenomenon seemed peculiar for the microglia cells have been beautifully demonstrated in the different stages of their evolution in cases of the experimental disease in monkeys.

"An attempt was made to study the inclusion bodies which have been described in the nuclei of the anterior horn cells especially in the experimental disease. In many cells of the anterior and posterior horns such bodies were found although some of them seemed to be nothing more than a clumping of the intranuclear network.

"Figure 23 shows a section of the lumbar region of the spinal cord in a man (R. M.) aged twenty who died after an illness of sixteen days. The spinal fluid examined on the fifth day of his illness was slightly cloudy with 180 cells per c. m. of which 76 per cent were polymorphonuclear. On the ninth day of his illness he was given 20 cc. of horse serum intraspinally and 20 cc. intramuscularly. The subsequent spinal taps showed a decrease in the cell count but details are lacking. Sections of the medulla, cervical, thoracic and lumbar regions of the cord showed a very severe and extensive anterior poliomyelitis with a considerable amount of leptomeningitis in the lumbar enlargement. This pial exudate is composed mostly of small, round, mononuclear cells (lymphocytes) and is to a great extent perivascular and more marked about the veins than the arteries. One thing worthy of note is that some of the exudate can be seen within the substance of an anterior nerve root at (*N*) about a vessel. The exudate is more marked in the pia over the anterior portion of the cord and in the anterior fissure than elsewhere. The lesion in the gray matter of the cord is more severe on one side than the other and affects the antero-lateral portion of the anterior horns most. Only one or two nerve cells remain in the anterior



PLATE XVII  
HUMAN POLIOMYELITIS

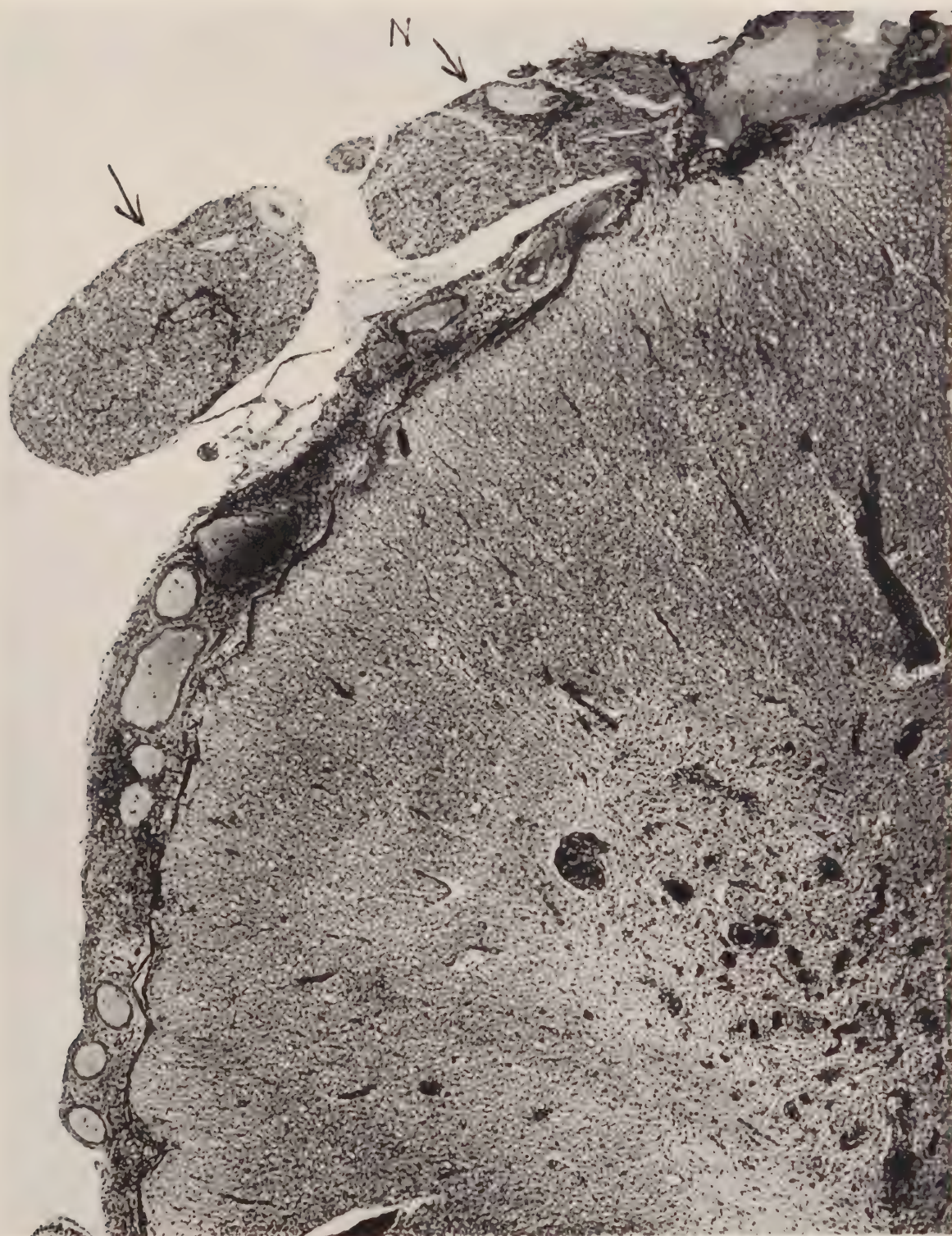


FIG. 23. *Spinal cord*, lumbar enlargement. Perivascular exudate in the pia. Treatment with horse serum. (Stevenson.)





horns and, indeed, even in the posterior horns there are very few cells left. The anterior horns are oedematous and mechanically broken up to a considerable extent. Perhaps we should say 'eaten up' for, as in some other pathological conditions of the nervous system, the microglia invade the damaged areas in such numbers and so hungrily that they are probably responsible for the disappearance of a great deal of tissue.

"The blood vessels of the anterior horns are greatly congested and show perivascular exudates of small, round cells. There are also many perivascular hemorrhages both in the anterior and posterior horns. The white matter is also affected by these exudates about the blood vessels radiating outwards towards the periphery of the cord especially from the anterior horns.

"Figure 24 is a high power photomicrograph of a blood vessel in one of the pial trabeculae in the region of the fissure of Rolando of the cerebral cortex in a case of anterior poliomyelitis which had been given serum. The patient (J. B.) was a boy of five years who died on the third day of his illness. He was described as a case of status lymphaticus constitution. On the second day of his illness the spinal fluid had 654 cells per cubic millimeter. Ten cc. of horse serum were given intraspinally and 20 cc. intravenously. The boy died about thirteen hours later. His cord showed a very extensive anterior poliomyelitis with a meningo-encephalitis as well. The perivascular pial exudate seen in the figure contains great numbers of polymorphonuclear cells. As in the previous case there was considerable leptomeningitis of the lumbar enlargement but polymorphonuclear cells predominated in this case. It was in this case also that we found the intranuclear bodies in the nerve cells of the anterior and posterior horns.

"Figure 25 shows a high power photomicrograph of an anterior horn cell with inclusion bodies in the nucleus. The cell is undergoing chromatinolysis and the nuclear membrane is wavy and becoming indistinct. The stain is hematoxylin and eosin with fixation in formalin.

"Figure 26 shows a posterior horn nerve cell stained with cresyl violet. Here again the nuclear membrane is indistinct and wavy and there are many intranuclear bodies which, in this instance, do not give the appearance of clumping of the nuclear network so much as in the previous figure.

"Figure 27 represents a section of the spinal cord in the case of a child (A. V.) of one year who became ill with poliomyelitis about the 30th August, 1931, and died of pneumonia on the 20th January, 1932. This



section is stained for myelin by Hortega's method and shows loss of myelin in the anterior horns and also in the antero-lateral columns of the white matter.

"Figure 28 is a photomicrograph of a portion of the anterior horn of the same case as in Figure 23. The section is stained with haematoxylin and sudan III and shows a great number of compound granular corpuscles within the anterior horn. The larger, rounded black masses are the fat-laden compound granular corpuscles. These large cells are the microglia cells which have become phagocytic and actively motile. Having devoured the broken down nerve cells and other tissue débris they remove it to the blood vessels of the vicinity where they may be seen to be collected in this figure. It is interesting to note that when this section was viewed as a whole under the low power, the fat laden granular corpuscles could be seen to be confined to the anterior horns and the white matter immediately adjacent to them, and to some extent in the antero-lateral columns of the white matter. They were completely absent in the posterior columns and the postero-lateral regions of the cord. This shows, of course, that the scavenging work to be done was in and about the anterior horns.

"Figure 29 is a photomicrograph of the same cord and region as shown in Figure 28 stained by Hortega's silver carbonate to show neuroglia. The astrocytes can here be seen in greatly increased numbers laying down a dense network of fibers to replace the nerve cells which have been destroyed by the disease and eaten up by the microglia cells.

"In one of our cases (M. F.), a woman of twenty-eight years, we were surprised to find definite degeneration in some of the nerve cells of the cerebral cortex. This woman's illness lasted about forty days. Sections of the spinal cord showed a typical anterior poliomyelitis. Clinically she had a flaccid paralysis of all four extremities, headache, drowsiness, and a stiff neck. She developed bulbar signs and was put in the respirator. She had received serum at home but the kind and method of administration are not known. Throughout her illness she had some temperature, as a rule about 100°F. although a few days before her death the temperature rose at times to 106°F. The large Betz cells seemed to suffer most and showed definite chromatolysis with eccentric and degenerated nuclei, etc. There was also a small amount of perivascular infiltration with mononuclear cells in this cortex.

"In the case of a child of one year (A. V.) who died of pneumonia about five months after an attack of poliomyelitis and who received no serum of any kind, the haematoxylin and eosin sections of the cord showed

PLATE XVIII  
HUMAN POLIOMYELITIS

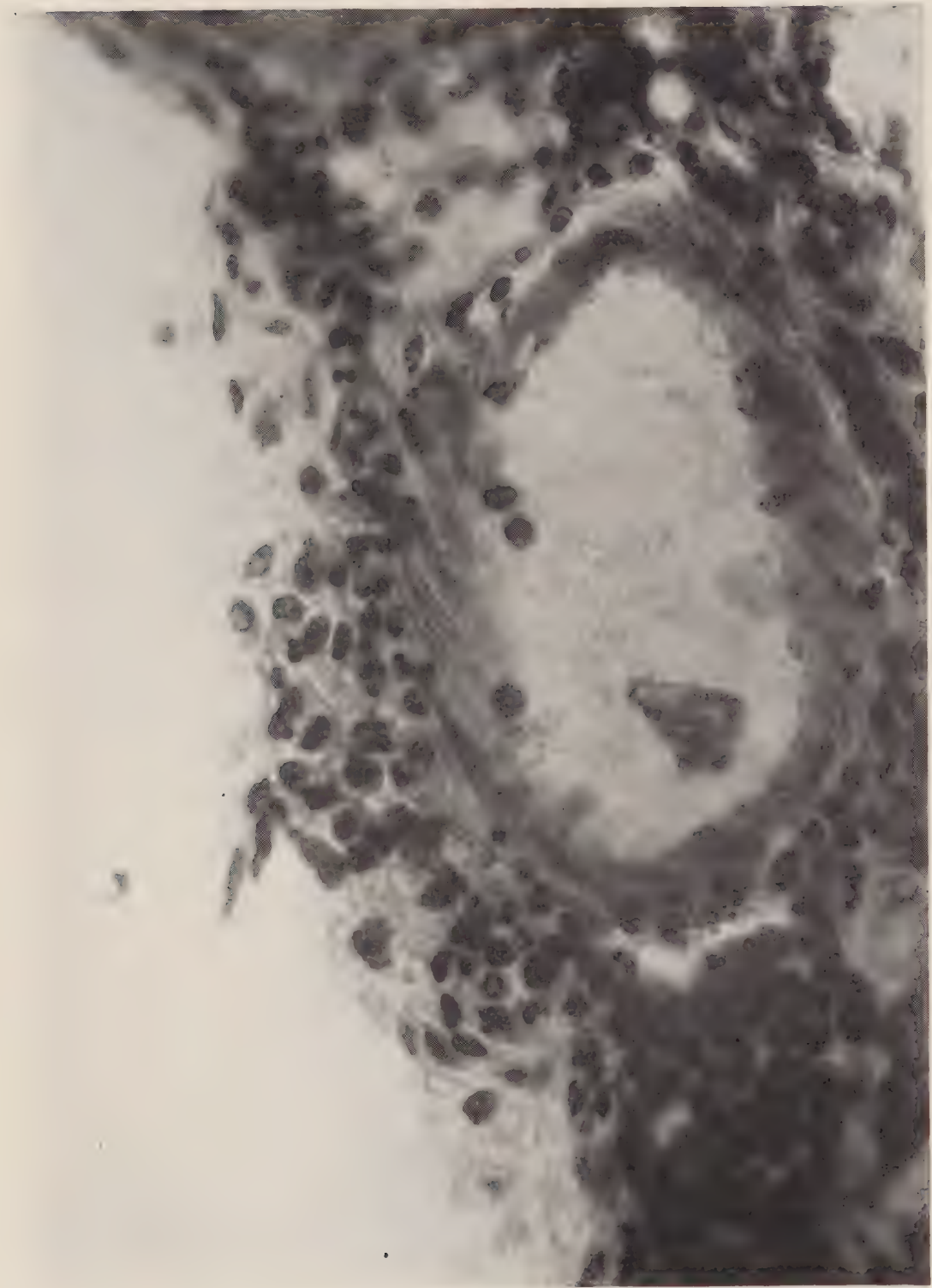


FIG. 24. *Meningo-encephalitis*. Perivascular pial exudate, containing polymorphonuclear cells. Treatment with horse serum. (Stevenson.)





PLATE XIX  
HUMAN POLIOMYELITIS

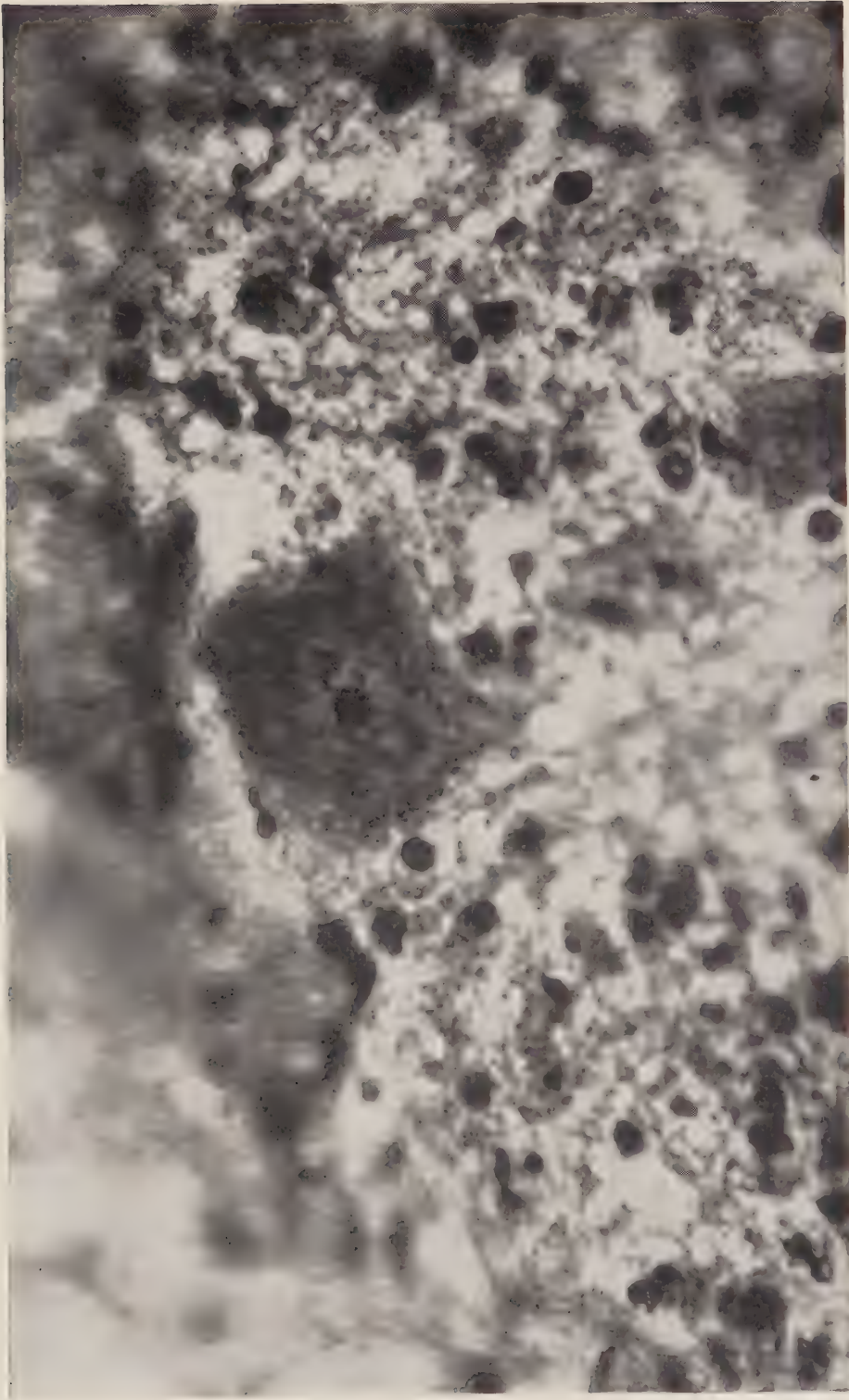


FIG. 25. *Anterior horn cell.* Intranuclear bodies. (Stevenson.)





PLATE XX  
HUMAN POLIOMYELITIS



FIG. 26. *Posterior horn cell.* Intranuclear bodies. (Stevenson.)





PLATE XXI  
HUMAN POLIOMYELITIS



FIG. 27. *Spinal cord.* Stage of repair, note loss of myelin in the anterior horns and in the antero-lateral columns of the white matter. *Hortega's method.* (Stevenson.)





PLATE XXII  
HUMAN POLIOMYELITIS

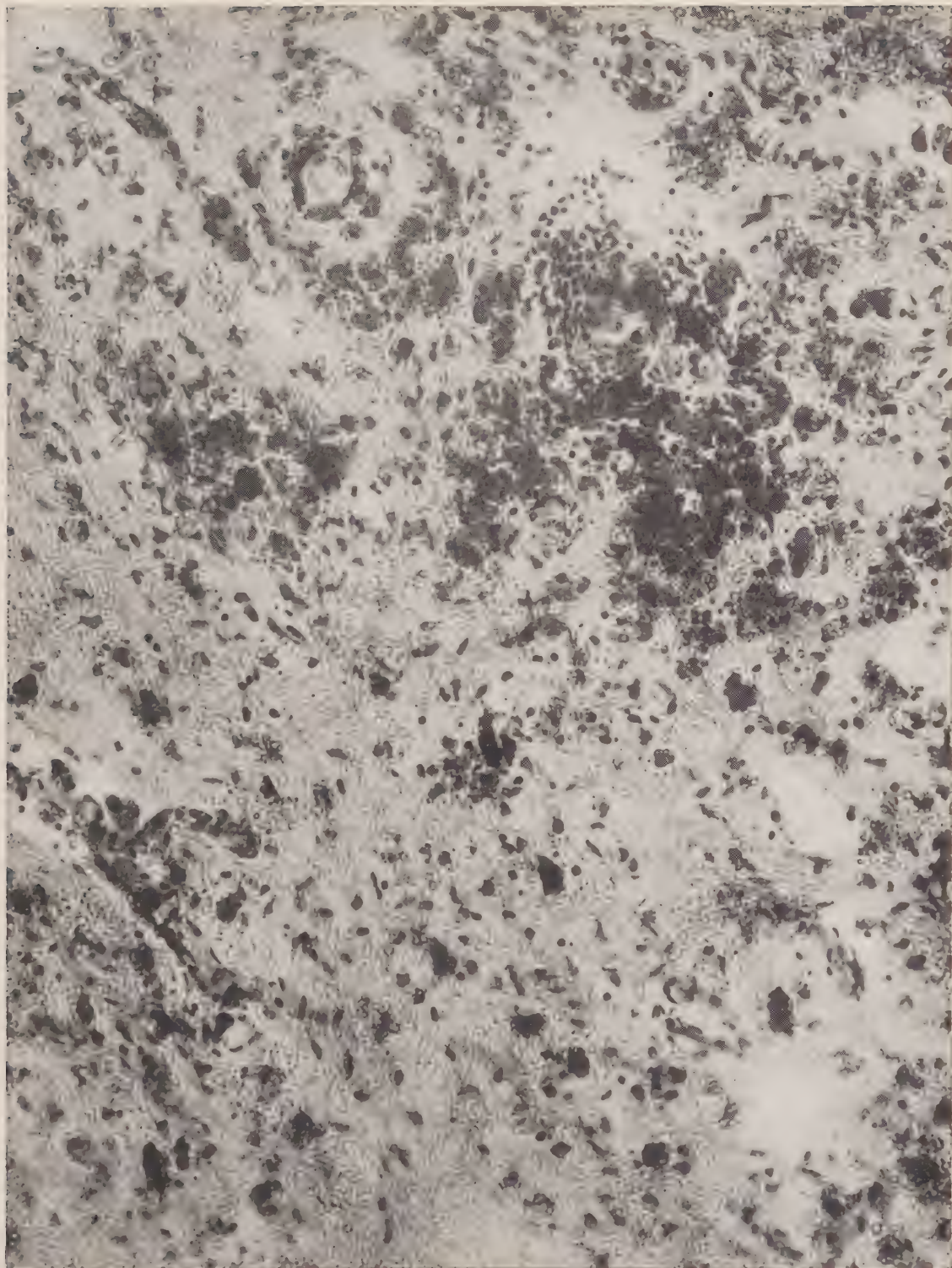


FIG. 28. *Anterior horn.* Stage of repair, showing compound granular corpuscles. Haematoxylin and sudan III. (Stevenson.)





PLATE XXIII  
HUMAN POLIOMYELITIS



FIG. 29. *Spinal cord.* Stage of repair, showing increased number of astrocytes. Hortega's silver carbonate stain for neuroglia. (Stevenson.)





no meningitis whatever but simply a loss in number of anterior and posterior horn cells with those cells which survived in a partial state of chromatolysis.

"One case (R) seemed to improve on antimeningococcic serum. The spinal fluid showed 1300 cells per c. m. of which 95 per cent were polymorphonuclear. Antimeningococcic serum was given intraspinally on at least four occasions and at each spinal tap the cells were reduced in number and the percentage of polymorphonuclears decreased. Sections of the spinal cord in this case showed no meningeal exudate whatever but a typical anterior poliomyelitis.

"In one other case observed only clinically—human convalescent serum seemed definitely to aggravate the meningeal signs present while antimeningococcic serum was immediately followed by improvement of them."

### STAGE OF REPAIR

The earliest pathological reports were based, as we have seen, upon the examination of cases of long standing. After the appearance of the disease in epidemic form and the consequent increased opportunities afforded students of obtaining autopsy material from acute cases further study of the residual lesions in the central nervous system was almost ignored. Wickman (W 21) gave only a brief description of the reparative phase "as from every point of view it is of much less interest than the acute stage." Schwalbe (1902, S 24) included in his summarized report of 22 autopsies, 14 in which the examination had been made at a period of from 5 months to 65 years after the onset of the paralysis. Lövegren (1905, L 61) described in detail one case of 2 years duration and Müller (1925, M 55), has included a brief discussion of this stage in his chapter on poliomyelitis in the *Handbuch der inneren Medizin*.

As recovery is less frequent in monkeys and the period of survival is brief in any event, lesions of long standing in these animals have not often been described. Levaditi and Stanesco (1910, L 53) examined the central nervous system, muscles, and peripheral nerves of 3 monkeys that lived 21, 29 and 67 days after the acute illness; Römer (1911, R 25; see also Müller, M 55) described the stage of repair in 1 that died 36 days after paralysis; and 1 animal of those studied by Hurst was killed on the thirty-fifth day. In 2 other animals surviving for 1, and 1½ years respectively Hurst (personal communication) could find no lesions other than a disappearance of anterior-horn cells, secon-



dary gliosis, and degeneration in the corresponding nerves and muscles. Warburg (1931, W 4) has recently discussed the persistent lesions in the central nervous system of 15 *Macacus rhesus* monkeys. These animals had received intracerebral inoculations, nasal instillations, or intralumbar or intracisternal injections in the course of immunization studies (Rhoads, R 10, R 11, R 12, R 13) and had been kept alive for periods varying from 19 to 309 days after the onset of symptoms.

In the stage of reparation, the process in the spinal form begins to localize macroscopically and microscopically more and more in the anterior horns. With widespread, irreparable involvement of the nervous tissue, the anterior horn becomes scarred; it shrinks and retracts on cross-section. Thus there develops the "atrophy of the anterior horns" recognized by Prévost and Vulpian as the anatomical basis of the residual infantile paralyses. Microscopically, reparation is signalized by the appearance of granule-containing cells. Absorption and removal of the cell-remnants commence; "the tissue is dissolved, melted and ingested by these granular cells" (Wickman). They gradually diminish in number but perivascular infiltration has been found present even as long as 2 years after the onset of paralysis (Von Kahl-den, K 3, K 4; Lövegren, 1905, L 61). Warburg (1931, W 4) has discussed the question as to whether the infiltration may be regarded as a sign of activity. In her series, inflammatory areas persisted in 4 animals that had made a good functional recovery.

There is proliferation of the neuroglia tissue: "its cells develop so many wide and much branched processes that they resemble seaweed-covered stones" (Wickman). Gradually a firm neuroglia scar is formed. The degree of cicatrization depends upon the extent and severity of the acute process.

Axis cylinders and anterior horn ganglion cells disappear in the interstitial round-cell infiltration. With disappearance of the tigroid bodies and vacuole formation the ganglion cells round out, become fatty and cloudy, and the neuro-fibrils become less without changing in form. Many wandering and small nucleated cells remove the débris. Round-cell infiltration is also found in the posterior horns and in Clarke's column.

Degeneration and atrophy of the anterior roots and of the muscles follow the destruction in the anterior horn.

As a result of the original disseminated process, secondary degeneration is found in the antero-lateral and cerebellar tracts and in the posterior columns.

Atrophy of the central convolutions, thought to be secondary to peripheral degeneration has previously been mentioned (see Sander, Rumpf, Colella, and Probst).

Warburg has emphasized the widespread character of the pathological changes. In general the intensity of the perivascular infiltrate and the destruction of the nerve cells were more marked in the cord. In both cord and mid-brain the anterior nuclei were more severely affected. Under the floor of the fourth ventricle, however, sensory and motor nuclei were equally involved. In the basal ganglia, the thalamus suffered more than the lenticular nucleus. Both motor and sensory cortex showed focal lesions.

The character of the alterations was interpreted by Warburg as belonging to two types: "(1) degenerative and inflammatory, including meningitis (negligible), perivascular and extra-adventitial infiltration, degeneration of the nerve cells and fiber tracts, and (2) reparative, including proliferation of microglia, astrocytes and capillaries."

Although the human infection is less severe than the experimental disease, the persistence of the lesions makes it probable, Warburg concludes, that "the process may continue to smoulder long after the acute symptoms have disappeared, thus suggesting that prolonged rest may be indicated before reconstructive therapy is begun."

A human case was observed in the Willard Parker Hospital during the New York epidemic of 1931 in which active lesions were demonstrated 2 months after the acute attack. A boy of 18 years developed typical poliomyelitis in October, 1931, with almost complete paralysis of both legs. Convalescence was uneventful until the middle of December when death occurred suddenly following a febrile period of 4 days. Necropsy showed an old process in the lumbar region and acute lesions in the medulla (Smith, personal communication).

### INTRACELLULAR PATHOLOGY

The observation that the development of "inclusion bodies" within the cells is characteristic of many virus diseases has led inevitably to a search for these objects in tissues affected by the virus of poliomyelitis. The Negri bodies of rabies and the Guarnieri bodies of vaccinia were well known when Bonhoff (1910, B 21) reported inclusion bodies in the neuroglia cells of the spinal cord of 2 human cases of poliomyelitis, in which death occurred at the acute stage (the exact interval after onset is not stated).

The objects were particularly numerous in the lumbar enlargement



and were seen best when stained by Lentz's modification of Mann's method. They were round or oval, or, in some cases, were drawn out to a sharp point and varied in size from minute red points to about 3 or 4 $\mu$  in diameter. As many as 5 of these bodies were counted in one nucleus. They were always surrounded by a distinct halo, sharply outlined. The largest ones showed 1 or 2 small, punctate black "Innenkörper."

The inclusions were found both in the gray and in the white matter of the cord, although they were less numerous in the latter location; in some sections, half of the glial cells contained inclusions. They were also observed in the nuclei of the cells infiltrating the adventitia, in the ependyma cells of the central canal, and in many of the round cells in the focal aggregations.

Bonhoff had not observed such inclusions in normal cords or in those obtained from other diseases, although the number of controls was not large. He believed, however, that the numerous examinations of spinal cords that had been made since the discovery of the Negri bodies in 1903 could, in a sense, be considered controls for these findings in poliomyelitis. Bonhoff concluded that the characteristics of these nuclear inclusions in the neuroglia cells, and especially the presence of the very small "Innenkörper" seen in a number of instances, indicated that they must be considered foreign objects (Fremdgebilde), specific for the disease in question.

Walter (1912, W 3) observed inclusions in large motor cells that were not badly deformed. They were not found in all the cells and in only 2 cases. The bodies stained with acid fuchsin, and lay in the protoplasm near the nucleus always surrounded by a clear halo and separated from the rest of the protoplasm by a thin, but definite membrane. Walter felt that his material was too scant to state that these objects were characteristic of poliomyelitis but their regular occurrence in the motor cells and their typical form suggested specificity.

Basophilic granules, varying from scarcely perceivable dots to the size of a coccus or even larger, were observed by Kraus and Gerlach (1928, K 30) in brain and cord sections of a monkey, killed on the seventh day after the development of paralysis. The granules were found in the gray and white matter in specimens stained according to Krogh and Heidenhain. They were extra-cellular, but occurred also in the plasma of the ganglion cells; some were like dust in the neuroglia; they were seen too in the walls of many blood vessels. No hypothesis was advanced by Kraus and Gerlach concerning the rela-

tion of these granular objects to the disease of poliomyelitis at this time. But later, Gerlach and Kress (1931, G 7) concluded that the granules were not specific for the diseases in which they had been observed (pseudo-rabies and poliomyelitis). In their opinion, these objects are physiological findings, occurring both within and without the ganglion cells in various species of animals and also in man. Comparative studies indicated that they may be looked upon as a waste pigment of lipoidal nature (lipofuscin, Lubarsh). These granules seem to be particularly numerous in the diseases mentioned. This might result, Gerlach and Kress suggested, from some specific injury to the nerve cells brought about by the neurotropic virus.

Paul (1928, P 4) attempted to verify their findings. He was able in cases of experimental and human poliomyelitis, and in normal controls, to demonstrate granules in varying numbers in the ganglion cells of the central nervous system, most abundant in the vagus nucleus. Their staining and micro-chemical properties, as well as the cell-topography, led Paul to the conclusion that he was dealing with lipofuscin, a normal constituent of ganglion cells.

While studying the lesions in the nasal mucous membranes of monkeys with the experimental disease, Stewart and Rhoads (1928, S 57) noted acidophilic intranuclear bodies in the epithelial cells of the respiratory mucosa. Isolated necroses of these cells were found in 17 of 31 monkeys that had been inoculated intracerebrally and killed at various stages of the disease. They were not found in 9 controls. These inclusion-like bodies were most frequently single and centrally placed, with the chromatin in a peripheral ring. Nothing to suggest a mulberry appearance was observed. The authors considered the nature of these nuclear bodies "uncertain." The lesion was not found in all of the inoculated monkeys and only isolated cells showed necrosis. These facts would argue against specificity. Further study, they felt, was necessary.

Recent reports by Covell (1930, C 28) and by Hurst (1931, H 41), however, make it seem more probable that specific inclusion bodies have been demonstrated. In the nucleus of ventral horn cells or cells of the medulla with marked degenerative changes, Covell observed definitely outlined acidophilic bodies, 0.25 to 3 $\mu$  in diameter, and with a distinct halo. Central nervous system tissues of 10 normal monkeys were compared with those obtained from 33 monkeys that had died of acute poliomyelitis or had been killed at various stages of the disease. The material was fixed in Zenker's and stained with Giemsa. The intra-



nuclear bodies were found in sections from all the animals that were killed at the onset of paralysis and were fairly numerous at this early stage but were diminished in number at later stages (1 to 3 weeks).

Hurst's study is in agreement with Covell's report. Tissues were fixed in sublimate-formol or Zenker-formol and stained most satisfactorily by Mallory's phloxin-methylene blue or Giemsa. The intranuclear bodies had a more distinct outline than the normal nodal masses and were frequently surrounded by a clear halo. They varied from fine granules to round objects 4 to 5 $\mu$  in diameter and were nearly always multiple in serial sections. In some instances small granules were attached to the surface of a larger body. With phloxin-methylene blue, the color varied from bright red to bluish pink; with Giemsa, it was dull red or pinkish purple. (Fig. 30.)

The inclusions were observed most frequently in the large anterior horn cells with marked but early degenerative changes, next in the smaller nerve cells of both the anterior and posterior horns, also in the nerve cells of the brain stem, and in the Betz cells of the motor cortex. They were never found in normal cells, in completely necrotic cells, or in glial cells.

These bodies were demonstrated in the tissues of 25 out of 28 monkeys with experimental poliomyelitis during the first 3 days of paralysis; material from the other 3 was obtained some time after death which may have accounted for the negative results. As noted by Covell, the number of the bodies present fluctuated with the stage of the disease; none were found in the 7 cases examined during the incubation period; on the first day of paralysis, they were sometimes present in 4 or 5 cells in one section; none were seen in monkeys examined 6 days, 1 month, and 1 year after the onset of paralysis. At a late stage of the disease, they were more numerous in the Betz cells than in the cord. They were also present in the cord from a human case and in material from the second passage but not from the first. None were found in the 24 controls examined; among these were 2 monkeys with rabies, 5 with vaccinal encephalitis and 1 human case of post-vaccinal encephalitis.

Hurst has concluded that "the bodies described are probably nuclear inclusions of the same order as those in herpetic encephalitis, Borna disease, etc.," and that "it seems possible that they may represent a nuclear reaction to the attack of virus." The fact that they have not been found during the incubation period agrees with Fairbrother and Hurst's finding (F 6) that the virus does not reach the cord, after intracerebral inoculation, until just before the onset of paralysis.

PLATE XXIV  
NUCLEAR INCLUSIONS IN POLIOMYELITIS

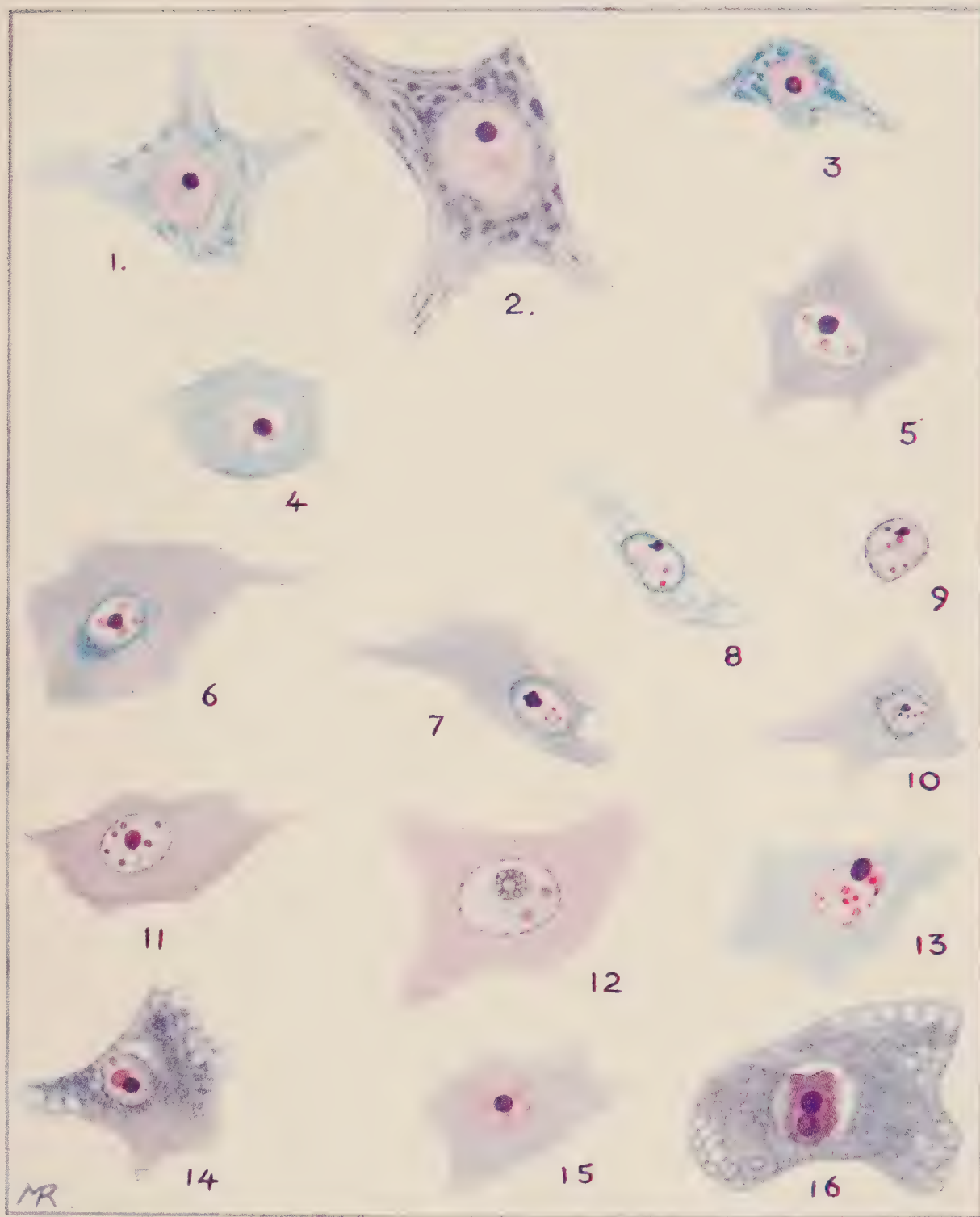


FIG. 30. With the exception of 12 all the drawings were made from the monkey tissues.  
 1, 3. Normal anterior-horn cells showing respectively nuclear acidophilic reticulum and masses and diffuse nuclear staining. Sublimate-formol: phloxin-methylene blue.  
 2. Normal anterior-horn cell with nuclear acidophilic reticulum and nodal mass Zenker-formol: Giemsa.  
 4, 6, 7, 10, 13. Anterior-horn cells from poliomyelitic cords showing nucleus partly or wholly devoid of acidophilic coagulum and containing inclusions in the shape of granules, spherules and spherules with granules attached to the surface. Sublimate-formol: phloxin-methylene blue.  
 5, 14. Similar appearances with Giemsa staining. Sublimate-formol and Zenker-formol respectively.  
 8, 9. Similar appearances in small cells of posterior horn. Sublimate-formol: phloxin-methylene blue.  
 11. Anterior-horn cell with inclusions. Formol-saline: Delafield's haematoxylin.  
 12. Anterior-horn cell from human case showing inclusions. Formol-saline: Delafield's haematoxylin and eosin.  
 15. Anterior-horn cell showing diffuse nuclear staining and several rather more intensely coloured inclusions. Zenker-formol: Giemsa.  
 16. Anterior-horn cell with shrunken, hyperchromatic, nucleus and inclusion poorly differentiated from remaining nuclear structure. Sublimate-formol: Giemsa. (Hurst.)





Inclusions similar to those observed by Stewart and Rhoads have recently been described by Covell (1932, C 29). They occurred not only in the nasal mucous membranes but also in the epithelial cells of the trachea, lungs, and bile ducts; they were seen in a few monkeys with experimental poliomyelitis and likewise in animals that had never been inoculated with the virus. These inclusions were formed of acidophilic particles clumped and fused together; in appearance, they were distinct from those found by this author and by Hurst in the injured nerve cells of monkeys with the experimental disease. The author concludes that the intranuclear inclusions found in the locations above mentioned are caused by some virus of low virulence, which produces no recognizable clinical symptoms. Their recognition is of interest because of employment of monkeys in experiments with such viruses as those of poliomyelitis, yellow fever, chicken-pox and measles.



## CHAPTER VII

# EPIDEMIOLOGY

### PART I. EPIDEMIOLOGY OF THE DISEASE

#### INCREASE IN LAST FORTY YEARS

A great deal of interest and apprehension has resulted from the increase in poliomyelitis and in the other infectious diseases of the central nervous system in the last forty years. There is a question as to whether this increase is real or only apparent. An editorial in the *Medical Officer* for May 14, 1932 (E 10), says, in regard to this increase in incidence: "It is well to consider whether this increase is genuine and, if it is, to what it may be due. Special attention directed against any disease always results in an immediate rise of apparent incidence, followed by a fall which, however, does not reach the low level the disease appeared to have had before it was specially scrutinized. If the attention results in some satisfactory means of prevention, a further fall occurs which may reach any level short of zero. The bulk of the preliminary rise is naturally due to unearthing missed and trivial cases, but also to the inclusion of doubtfuls, which formerly were attributed to other conditions. The fall following the rise is due to stabilization of the dividing line which cuts across the doubtfuls. Whereas before the special attention all doubtfuls are excluded, and in the first phase of attention all doubtfuls are included, experience teaches us to separate this class more accurately into positives and negatives. In the past poliomyelitis was synonymous with infantile paralysis, now it is not, for we know that the disease does occur without the production of paralysis. Perhaps one third of the cases now rightly diagnosed as poliomyelitis do not end in paralysis, and so we should expect the incidence of the disease to have increased, apparently by one-third. The increase has, however, been much greater than this, suggesting that the disease is actually more frequent than it used to be."

Undoubtedly the fact that poliomyelitis became a reportable disease in most countries of Europe and America between 1910 and 1920 has made comparison of incidence before and since that time unprofitable. (The League of Nations Monthly Epidemiological Report for February 15, 1930, gives a good summary of laws governing compulsory notification in the various countries, when adopted, etc.)

CHART III

# POLIOMYELITIS MORBIDITY RATES UNITED STATES AND OTHER COUNTRIES

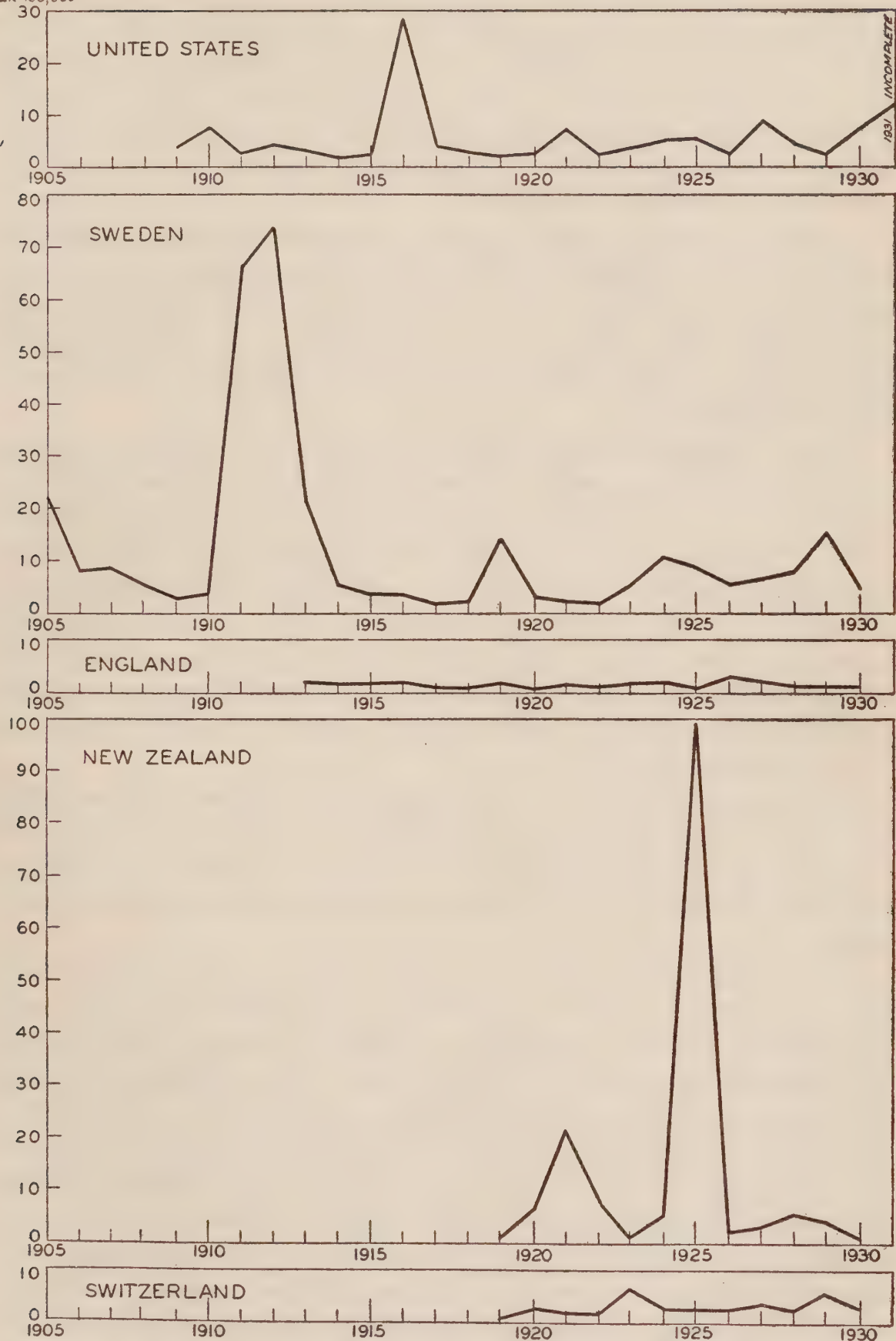
CASE RATE  
PER 100,000

CHART III. Figures for the United States from Public Health Reports, and from League of Nations, Monthly Epidemiological Reports, February 15, 1930. Figures for other countries from League of Nations, Monthly Epidemiological Reports, February 15, 1930, and later issues.



In spite of these considerations as to reporting, however, it is generally agreed that the increase in incidence is real, and that the greater interest, compulsory reporting, and better diagnosis, are primarily the effects, rather than the cause of the increase. The League of Nations (L 17) concludes that: "Poliomyelitis became notifiable in different countries only when the frequency and gravity of the disease made such a measure necessary."

In spite, however, of this interest, and of the resulting speculation with which the literature is filled, no adequate explanation of this increase has been given. Why poliomyelitis, occasional sporadic cases of which have been known to have occurred for many years throughout Europe and America, should have suddenly assumed epidemic proportions, is unknown.

Possible changes in each of the fundamental epidemiological variants—the host, the virus, and the transmission factor—have been offered as explanations of this increase. The various lines of reasoning are, briefly:

(1) *Changes in the Host.* Some epidemiologists have concluded that the resistance of the host has altered. MacNalty (M 10) especially has supported the theory that the strain of modern life is responsible for an increasing vulnerability of the central nervous system, and for the increased incidence of infections affecting it. The different factors which influence susceptibility in populations is considered in the Section on the *Epidemiology of the Host*.

(2) *Changes in the Virus.* The hypothesis has been advanced that the virus of poliomyelitis has undergone some mutation. This might have been in the nature of (a) an increased infectivity, (b) a generally increased virulence, or (c) an increased affinity for the central nervous system.

(a) A change in the virus in the nature of an increased infectivity has been argued by some to account for the increased incidence. Such an increased infectivity would be at variance with the theory of latent immunization (see under *Contagiousness*). Since poliomyelitis, when it first assumed epidemic proportions, exhibited the epidemiological characteristics of a disease falling on immunized or "salted" populations—a low morbidity rate, lower in urban than in rural outbreaks, an incidence affecting chiefly the early ages, earlier in urban than in rural outbreaks, the explanation of an increased infectivity has been rejected by the proponents of this theory. The age incidence of epidemic encephalitis has, on the contrary, been suggestive of an organism striking entirely unimmunized populations.

Flexner and Amoss (F 29) reported one strain which gained through repeated passage an adaptation to monkeys, subsequently lost, and later regained this adaptation.

(b) No rise or fall of virulence of human strains has been shown to be synchronized with epidemic prevalence of poliomyelitis, and so far as we can say, the viruses from different epidemics have been equally virulent for monkeys.

There are some who believe that the pandemic of poliomyelitis which has affected a great part of the world originated with the Scandinavian epidemic of 1905. It is suggested that a fresh vigorous strain of virus has spread from there to other countries. The fact is cited that some 42,000 Scandinavian immigrants arrived in the United States about 1907, a year that marked the first large epidemic in this country. We know of no study which has shown the relation between the distribution of these Scandinavian immigrants and the distribution of the wave of poliomyelitis in the Middle West which followed.

Park (personal communication) has encountered one strain which increased in virulence for monkeys when passed rapidly from animal to animal.

(c) That poliomyelitis and epidemic encephalitis are not new diseases but are exhibiting an increased affinity for the central nervous system is held by a number of epidemiologists. Dale (D 2) says, "Many organisms exhibit strains that are biologically distinguishable. They must have evolved from a common progenitor, and that evolution must be continuous . . . It is not far-fetched to think that the occurrence of epidemic poliomyelitis is due to the development of a more definite neurotropic tendency by a strain of an already widespread virus. The march of that particular strain, unnoticed before, would then become evident as a prevalence of poliomyelitis."

(3) *Changes in the Transmission Factor.* The factors influencing transmission of poliomyelitis are not agreed upon. If person to person contact is conceded, as it is by many, it seems reasonable that, with the development of many varieties of rapid transportation and with the constant acceleration of human communication, both international and within more limited areas, there should be an increase of diseases thus spread. This increased contact has especially affected rural life. Not only does this intercommunication add to the facilities for infection, but it adds complexity to efforts to trace infection. Stallybrass (S 53) says, "Given the precedent conditions necessary for infection then the probability of transmission increases proportionately to the extent to which aggregation and dispersal occur."



This argument gains weight from the experiments on mice of Topley and his co-workers. These authors have shown that within isolated mouse communities, an epidemic tends to die out, leaving the survivors and the organisms in a state of apparent equilibrium. The infection will flare up again on the addition to the community of fresh susceptibles, not only the latter being affected but also the survivors of the previous outbreak. The regular importation of fresh susceptibles will maintain the epizootic indefinitely, the disease waxing and waning.

#### GEOGRAPHIC DISTRIBUTION

Poliomyelitis is widely distributed. No country for which records are available is known to be entirely free from sporadic cases. Lavin-der, Freeman and Frost (L 16) stated in 1918: "Poliomyelitis has become so widespread as to make it evident that this disease is independent of any special climatic or other conditions which are peculiar to any restricted part of the globe."

While poliomyelitis is thus widely disseminated in endemic form, large epidemics have been almost entirely confined to the colder climates.

**Notification.** Reference has previously been made to the fact that the figures for the various countries are not comparable before and after the disease was made notifiable. The following information is given as to the countries in which notification is compulsory. Somewhat more complete data can be obtained from the League of Nations, Monthly Epidemiological Report for February 15, 1930, from which this summary is taken:

1. In the following countries, poliomyelitis is a notifiable disease (where available from the above report, the date at which reporting was made obligatory is given): Australia, adopted in most states, at varying times; Austria, province of Carinthia only, 1913; Bulgaria, 1927; Canada, in most provinces, at varying dates; Denmark; England, 1924; Finland; France, 1916; Germany, in practice generally reported, compulsory in Prussia, 1924, and Saxony, 1923; Hungary; Irish Free State; Italy; Netherlands; New Zealand, 1920; Norway, 1904; Poland, 1927; Portugal, 1901; Roumania, 1927; Scotland; Spain, 1916; Sweden, 1905; Switzerland, 1914; United States of America, notifiable in most states, in most 1909 and 1910; United States of Soviet Russia.

2. Poliomyelitis is not notifiable in Belgium; Greece; Czechoslovakia; Turkey; Japan.

Not only are the figures for poliomyelitis before and since notification was made compulsory, not comparable, but it is true also that the en-

CHART IV  
POLIOMYELITIS CASE RATES  
UNITED STATES, 1915 - 1929

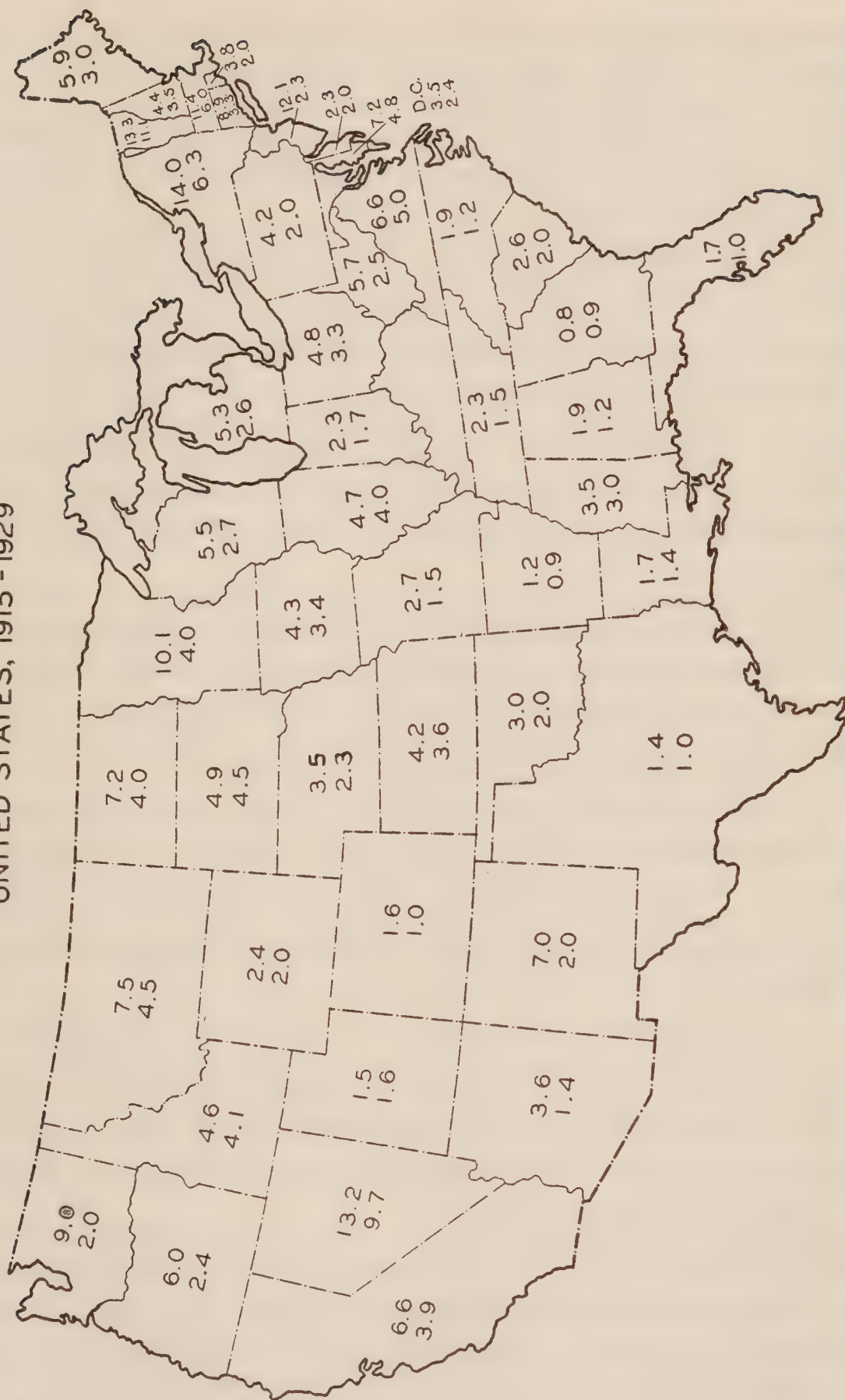


CHART IV. Poliomyelitis, United States, 1915-1929. The upper figures represent the mean, and the lower the median case rate per 100,000 for these years. (Figures from United States Public Health Reports, The Notifiable Diseases, Prevalence in States, 1915-1929.)



demie rates of countries which have suffered epidemics cannot be compared with endemic rates in those countries which have not. The interest which follows upon epidemics is reflected in the reporting in inter-epidemic periods, while in countries which have not so suffered, physicians are unalert to the early manifestations and the desirability of complete reporting.

**Effect of Latitude.** Whatever is the nature of the factor which determines endemic incidence and epidemicity of poliomyelitis, it varies with latitude. In general, both the endemic rate and the frequency and severity of the epidemics increase with distance from the Equator, both in the Northern and Southern hemispheres. Northern Europe and the Northern United States and Canada are the areas from which most cases have been reported. The corresponding zone in the Southern hemisphere is largely occupied by water, but the incidence in New Zealand, Australia, and the Southernmost parts of South America and Africa is comparable.

This is probably not universally true, as vast portions of China and Manchuria have a climate which at least so far as temperature is concerned is similar to that of Europe and northern America. Yet poliomyelitis is, according to the few references in the literature, a rare disease in China. Sporadic cases occur, but so far no epidemics have been known (Zia, Z 4; Jefferys and Maxwell, 1929, J 2).

**Tropics.** Small epidemics have been known to occur in the tropics: Lebrede and Recio (L 22) reported an epidemic of 140 cases in the Province of Santa Clara, Cuba, in 1909; three epidemics have been reported in Melanesia (these are discussed under *Age, Virgin Soil Epidemics*); Morales (M 44) reported an outbreak of 10 cases in Porto Rico in 1928.

**United States.** The incidence in the United States increases as one proceeds North. Not only is the endemic rate higher in the Northern states, but superimposed on this are frequent epidemics of varying severity, which are almost unknown in the South. (See Chart IV.) The Southern part of the United States has suffered a few epidemics, Texas in 1913, Louisiana in 1930.

**Endemic and Epidemic Rates.** At its worst, poliomyelitis is a disease of low incidence. Even in the countries in which the disease has been most prevalent the rates have been low. Lavinder, Freeman and Frost (L 16) say: "Even during so-called epidemics poliomyelitis has characteristically a small incidence in the total population. To be sure, instances are not wanting of epidemics in which a large proportion,

over 1 per cent, of the total population has been attacked, but these are rather exceptional instances and are practically confined to outbreaks in small towns and small rural areas. In a large aggregation of people, such as the population of a city with over 100,000 inhabitants, a county, or a state, epidemics seldom attack more than one in a thousand of the population, often not more than one in two to four thousand. Even New York City, in the severe epidemic of 1916, had a general prevalence of less than 3 per 1,000 of population. The incidence of poliomyelitis, therefore, even in epidemics is frequently less than the usual annual incidence of several of the more common endemic infectious diseases in the same communities, and, strikingly less than the incidence which these common diseases frequently attain during epidemics."

Lavinder, Freeman and Frost (L 16) did, however, suggest that "while the incidence among a population affected by poliomyelitis, even in its severest epidemic form, is usually not high, yet this disease possesses not infrequently the power to spread widely—in fact to become pandemic in a country. It has been suggested that an epidemic of infectious disease may be viewed as the resultant of two excursions, a vertical one representing the heaping up of cases in any locality, as usually shown plotted on a chart, and a lateral one representing the extent of territory covered—the geographic distribution. Epidemic diseases not infrequently show decided variation in these two movements. Certain of them, like dengue for example, show a most striking vertical movement along with a very limited lateral movement. Poliomyelitis has exhibited a significant power of lateral movement, and, up to the present time, in much greater degree than its power of vertical excursion."

This "creeping tendency," as Dale (D 2) calls it, is suggestive of a limiting factor of host resistance, a low but widely spread population at risk, and a widespread virus.

*United States.* A certain amount of poliomyelitis occurs in every state of the United States every year. This is represented by the endemic rate of the disease for that state. Superimposed upon this, there may or may not occur, at varying intervals, epidemics.

The various states have shown individual peculiarities in both the endemic and the epidemic prevalence of poliomyelitis. In Table 11, we have given a brief summary of the experience of each state with poliomyelitis. The annual case rates per 100,000 population, as reported in the Public Health Reports (U 4), were tabulated for each state for such of the years, 1915–1929, as were available. The mean and the median case rates for each state were computed.



TABLE 11

POLIOMYELITIS INCIDENCE IN STATES OF UNITED STATES, MEAN AND MEDIAN RATES PER 100,000 POPULATION, WITH RATIO OF MEDIAN TO MEAN RATE\*

| STATE                     | NUMBER<br>OF YEARS<br>REPORTING | MEAN<br>RATE PER<br>100,000 | MEDIAN<br>RATE PER<br>100,000 | RATIO,<br>MEDIAN TO<br>MEAN RATE |
|---------------------------|---------------------------------|-----------------------------|-------------------------------|----------------------------------|
| Maine.....                | 14                              | 5.9                         | 3.0                           | 1.9                              |
| New Hampshire.....        | 10                              | 4.4                         | 3.5                           | 1.3                              |
| Vermont.....              | 14                              | 13.3                        | 1.1                           | 1.2                              |
| Massachusetts.....        | 14                              | 11.4                        | 6.0                           | 1.9                              |
| Connecticut.....          | 15                              | 8.9                         | 3.3                           | 2.7                              |
| Rhode Island.....         | 13                              | 3.8                         | 2.0                           | 1.9                              |
| New York.....             | 15                              | 14.0                        | 6.3                           | 2.2                              |
| New Jersey.....           | 15                              | 12.1                        | 2.3                           | 5.3                              |
| Delaware.....             | 9                               | 2.3                         | 2.0                           | 1.1                              |
| Pennsylvania.....         | 14                              | 4.2                         | 2.0                           | 2.1                              |
| Maryland.....             | 15                              | 7.2                         | 4.8                           | 1.5                              |
| Virginia.....             | 15                              | 6.6                         | 5.0                           | 1.3                              |
| District of Columbia..... | 15                              | 3.5                         | 2.4                           | 1.4                              |
| West Virginia.....        | 12                              | 5.7                         | 2.5                           | 2.3                              |
| Ohio.....                 | 15                              | 4.8                         | 3.3                           | 1.5                              |
| Kentucky.....             | Not reported                    |                             |                               |                                  |
| Indiana.....              | 14                              | 2.3                         | 1.7                           | 1.4                              |
| Illinois.....             | 13                              | 4.7                         | 4.0                           | 1.2                              |
| North Carolina.....       | 11                              | 1.9                         | 1.2                           | 1.6                              |
| South Carolina.....       | 9                               | 2.6                         | 1.0                           | 2.6                              |
| Georgia.....              | 8                               | 0.8                         | 0.9                           | 0.9                              |
| Florida.....              | 12                              | 1.7                         | 1.0                           | 1.7                              |
| Tennessee.....            | 6                               | 2.3                         | 1.5                           | 1.5                              |
| Alabama.....              | 13                              | 1.9                         | 1.2                           | 1.6                              |
| Mississippi.....          | 15                              | 3.5                         | 3.0                           | 1.2                              |
| Louisiana.....            | 14                              | 1.7                         | 1.4                           | 1.2                              |
| Texas.....                | 6                               | 1.4                         | 1.0                           | 1.4                              |
| Arkansas.....             | 5                               | 1.2                         | 0.9                           | 1.3                              |
| Oklahoma.....             | 4                               | 3.0                         | 2.0                           | 1.5                              |
| Michigan.....             | 15                              | 5.3                         | 2.6                           | 2.0                              |
| Wisconsin.....            | 15                              | 5.5                         | 2.7                           | 2.0                              |
| Minnesota.....            | 15                              | 10.1                        | 4.0                           | 2.5                              |

\* The data from which this table has been compiled are taken from the United States Public Health Reports, The Notifiable Diseases, Prevalence in States, 1915-1929.

TABLE 11—*Concluded*

| STATE             | NUMBER<br>OF YEARS<br>REPORTING | MEAN<br>RATE PER<br>100,000 | MEDIAN<br>RATE PER<br>100,000 | RATIO,<br>MEDIAN TO<br>MEAN RATE |
|-------------------|---------------------------------|-----------------------------|-------------------------------|----------------------------------|
| Iowa.....         | 13                              | 4.3                         | 3.4                           | 1.3                              |
| Missouri.....     | 6                               | 2.7                         | 1.5                           | 1.8                              |
| Kansas.....       | 13                              | 4.2                         | 3.6                           | 1.2                              |
| Nebraska.....     | 12                              | 3.5                         | 2.3                           | 1.5                              |
| South Dakota..... | 12                              | 4.9                         | 4.5                           | 1.1                              |
| North Dakota..... | 12                              | 7.2                         | 4.0                           | 1.8                              |
| Montana.....      | 14                              | 7.5                         | 4.5                           | 1.7                              |
| Wyoming.....      | 10                              | 2.4                         | 2.0                           | 1.2                              |
| Colorado.....     | 11                              | 1.6                         | 1.0                           | 1.6                              |
| New Mexico.....   | 10                              | 7.0                         | 2.0                           | 3.5                              |
| Arizona.....      | 8                               | 3.6                         | 1.4                           | 2.6                              |
| Nevada.....       | 7                               | 13.2                        | 9.7                           | 1.4                              |
| Utah.....         | 5                               | 1.5                         | 1.6                           | 0.9                              |
| Idaho.....        | 7                               | 4.6                         | 4.1                           | 1.1                              |
| California.....   | 15                              | 6.6                         | 3.9                           | 1.7                              |
| Oregon.....       | 15                              | 6.0                         | 2.4                           | 2.5                              |
| Washington.....   | 14                              | 9.0                         | 2.0                           | 4.5                              |

The median case rate, that is, the rate for that year of which half the years showed a greater, and half the years showed a lesser rate gives an index of the endemic incidence—the “annual Expectancy.”

The mean, or arithmetic average, rate per 100,000 adds to this endemic rate the extremes which have occurred. It represents, therefore, the total experience, expected and exceptional, of each state.

The ratio between the median and the mean rate may be taken as an index of the epidemicity. Practically, it indicates the frequency and intensity of the epidemics.

A study of Table 11, and Chart IV, which presents these facts graphically, will reveal that in general both the median and the mean rate increase as we proceed North, although the tendency is not strictly regular. While the median rate increases gradually with latitude, this increase is by no means so marked as is the increase in the average rate. That is to say, the endemic incidence is lower in the South, and it has also been free from large outbreaks. In the North, on the other hand, the average has been dominated by a few epidemic years. In New York City and the surrounding states, for example, the averages have



been largely submerged in the figures for the 1916 epidemic. The addition of the 1931 figures will make this even more pronounced.

The states having endemic rates (*i.e.*, median rates for reported years) of 5.0 per 100,000 or over have been Nevada, Virginia, New York, Vermont, and Massachusetts. Those having average rates of 7.0 per 100,000 or over per year have been Washington, Nevada, Montana, North Dakota, New Mexico, Minnesota, Maryland, New Jersey, Connecticut, New York, Vermont, and Massachusetts.

CHART V  
POLIOMYELITIS  
BY SIZE OF COMMUNITY  
NEW YORK STATE, 1915 - 1924

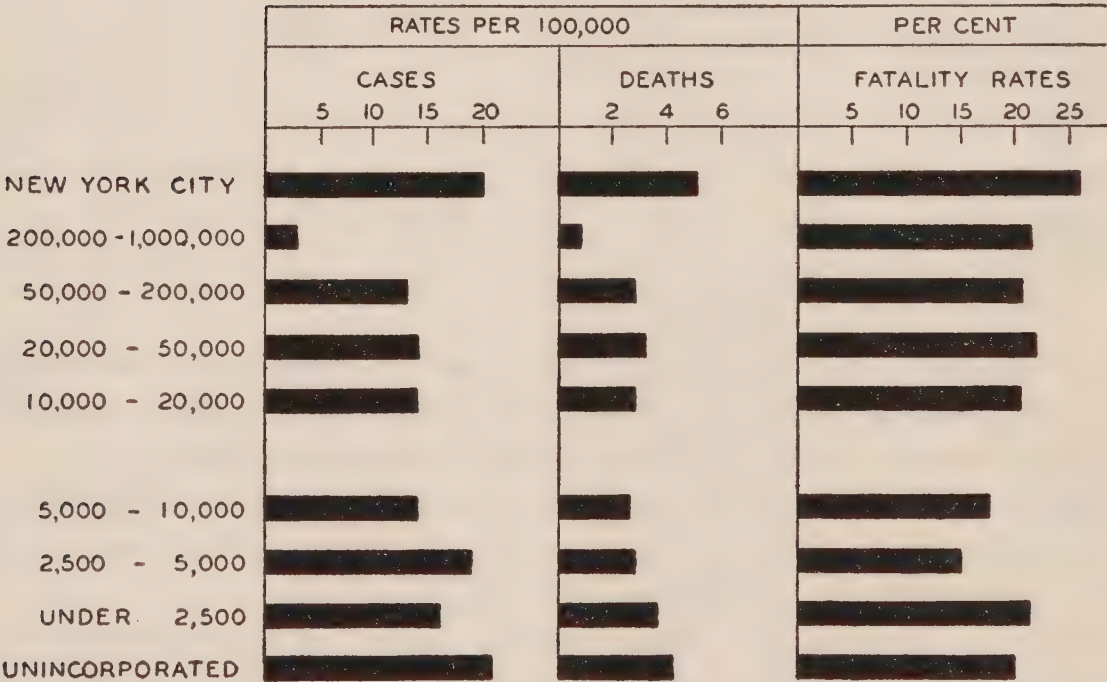


CHART V. From Godfrey, American Journal of Public Health 18: 630, 1928.

**Rural and Urban Incidence.** Wickman (W 21) pointed out, in the Swedish epidemic of 1905, that poliomyelitis seemed preferably to attack places lying far away from the large centers, seeming indeed to evade the cities and more densely populated sections. This observation has been corroborated in many epidemics since. Once an epidemic is established, the rural incidence tends to exceed the urban. As Lavinder, Freeman and Frost (L 16), moreover, point out: "This has been found true not only when individual small towns are compared with large cities, but also for groups of all the smaller towns or all the rural popu-

lation of a state, compared with all the large cities of the same area. The proportionately greater rural prevalence has, in fact, been so constant as to be unmistakably due not to mere chance but to some fundamental law. It is to be remembered, however, that this applies to epidemics; whether or not the same is true of the endemic or sporadic occurrence of the disease is not fully established.” Apparently in some instances it is. Godfrey (G 10) has furnished data on the distribution of cases and deaths in New York State for the years 1915–1924. In

TABLE 12  
ANTERIOR POLIOMYELITIS IN MASSACHUSETTS—1916–1929; CASE RATES PER 100,000 BY CERTAIN POPULATION GROUPS\*

| YEAR    | STATE | Over<br>500,000<br>(Boston) | 100,000–<br>500,000 | 50,000–<br>100,000 | 25,000–<br>50,000 | 10,000–<br>25,000– | 5,000–<br>10,000 | 2,500–<br>5,000 | UNDER<br>2,500 |
|---------|-------|-----------------------------|---------------------|--------------------|-------------------|--------------------|------------------|-----------------|----------------|
| 1916    | 51.6  | 65.8                        | 31.9                | 54.5               | 63.8              | 53.5               | 44.9             | 42.0            | 45.9           |
| 1917    | 4.6   | 1.7                         | 4.4                 | 5.4                | 9.0               | 3.2                | 5.6              | 4.3             | 3.9            |
| 1918    | 2.6   | 1.9                         | 4.1                 | 2.2                | 2.2               | 2.7                | 1.2              | 3.6             | 3.0            |
| 1919    | 1.7   | 1.7                         | 1.8                 | 2.2                | 0.8               | 1.9                | 2.7              | 1.1             | 1.5            |
| 1920    | 18.0  | 25.4                        | 7.2                 | 16.7               | 25.9              | 17.9               | 19.4             | 9.6             | 14.9           |
| 1921    | 5.9   | 6.2                         | 2.7                 | 5.7                | 8.9               | 8.4                | 6.0              | 4.4             | 4.0            |
| 1922    | 5.4   | 6.2                         | 5.0                 | 6.7                | 3.3               | 6.5                | 5.3              | 3.7             | 6.0            |
| 1923    | 5.5   | 5.2                         | 7.8                 | 5.7                | 4.6               | 4.9                | 4.8              | 1.5             | 5.6            |
| 1924    | 6.8   | 7.2                         | 8.9                 | 4.8                | 6.3               | 4.3                | 9.7              | 7.3             | 3.6            |
| 1925    | 4.0   | 5.0                         | 2.6                 | 3.7                | 4.8               | 5.5                | 3.1              | 2.9             | 3.1            |
| 1926    | 5.8   | 1.7                         | 9.8                 | 5.9                | 5.2               | 7.0                | 3.2              | 4.7             | 5.6            |
| 1927    | 27.8  | 34.9                        | 20.8                | 21.1               | 42.0              | 24.9               | 24.0             | 20.2            | 36.3           |
| 1928    | 10.0  | 7.3                         | 6.1                 | 11.2               | 28.4              | 5.9                | 10.4             | 9.6             | 5.6            |
| 1929    | 2.7   | 4.0                         | 2.3                 | 2.7                | 2.1               | 2.5                | 1.6              | 3.9             | 3.3            |
| Mean... | 10.9  | 12.4                        | 8.2                 | 10.6               | 14.8              | 10.7               | 10.1             | 8.5             | 10.2           |

\* Forsbeck and Luther, New England J. Med., 203: 1115–1121, 1930.

Chart V will be seen the case and death rates for poliomyelitis according to the size of community in which they occurred. He explains that “the relatively high case and death rates in New York City are due entirely to the great epidemic of 1916. Since then the highest case rate in New York City has been 10 per 100,000 and the highest death rate 2.5 per 100,000 . . . The remarkable feature in the distribution of poliomyelitis by size of community is the high case and death rate which prevailed in places of less than 5,000 population. I wish to point out also that the case rate, as well as the death rate, was higher in the unincorporated towns than in the groups of denser population.”



Over a period of years, however, the average rates tend to be equalized. Smaller places are more seriously affected when an epidemic becomes established, but this happens less frequently than in the cities.

In Tables 12 and 13 are given the case and death rates for various communities of Massachusetts, classified by density of population for a period of 14 years, 1916–1929. It will be seen that while the difference in the various groups is not great, Boston has had the highest death rate in the state, and with one exception, the highest case rate.

TABLE 13  
ANTERIOR POLIOMYELITIS IN MASSACHUSETTS—1916–1929; MORTALITY RATES  
PER 100,000 BY CERTAIN POPULATION GROUPS\*

| YEAR    | STATE | Over<br>500,000<br>(Boston) | 100,000–<br>500,000 | 50,000–<br>100,000 | 25,000–<br>50,000 | 10,000–<br>25,000 | 5,000–<br>10,000 | 2,500–<br>5,000 | UNDER<br>2,500 |
|---------|-------|-----------------------------|---------------------|--------------------|-------------------|-------------------|------------------|-----------------|----------------|
| 1916    | 12.1  | 21.6                        | 5.2                 | 15.2               | 11.8              | 11.3              | 8.3              | 6.7             | 10.6           |
| 1917    | 1.4   | 0.7                         | 2.0                 | 0.7                | 2.0               | 1.3               | 1.4              | 1.1             | 1.0            |
| 1918    | 1.0   | 1.2                         | 1.1                 | 0.7                | 0.7               | 0.9               | 0.3              | 1.6             | 1.5            |
| 1919    | 0.4   | 0.4                         | 0.7                 | 0.2                | 0.0               | 0.7               | 0.6              | 0.0             | 0.0            |
| 1920    | 3.7   | 6.3                         | 1.9                 | 3.6                | 3.7               | 2.8               | 5.2              | 2.1             | 3.0            |
| 1921    | 1.2   | 1.7                         | 0.1                 | 0.8                | 1.4               | 2.1               | 1.8              | 1.1             | 1.0            |
| 1922    | 0.8   | 1.4                         | 1.0                 | 0.7                | 0.9               | 0.2               | 0.9              | 0.0             | 0.5            |
| 1923    | 0.9   | 1.2                         | 1.2                 | 0.4                | 1.2               | 0.2               | 0.0              | 1.5             | 1.5            |
| 1924    | 0.7   | 0.8                         | 0.4                 | 0.0                | 1.2               | 0.4               | 1.2              | 0.5             | 1.0            |
| 1925    | 1.3   | 1.4                         | 0.5                 | 0.2                | 2.3               | 1.2               | 1.7              | 1.4             | 2.6            |
| 1926    | 1.0   | 0.9                         | 1.6                 | 0.8                | 0.5               | 1.8               | 0.3              | 1.0             | 0.0            |
| 1927    | 4.0   | 8.1                         | 3.5                 | 2.0                | 4.1               | 1.9               | 2.9              | 2.7             | 4.0            |
| 1928    | 1.5   | 1.9                         | 1.0                 | 3.2                | 2.5               | 0.4               | 0.3              | 1.5             | 2.0            |
| 1929    | 0.5   | 1.1                         | 0.3                 | 0.4                | 0.4               | 0.3               | 0.5              | 0.0             | 0.5            |
| Mean... | 2.2   | 3.5                         | 1.5                 | 2.1                | 2.3               | 1.8               | 1.8              | 1.5             | 2.1            |

\* Forsbeck and Luther, New England J. Med., 203: 1115–1121, 1930.

SEASONAL INCIDENCE

Both in its endemic and epidemic prevalence, clinical poliomyelitis is characteristically a disease of summer and early fall. Although sporadic cases and even epidemics may occur during any month of the year, the periods, July to October in the Northern hemisphere, and January to April in the Southern hemisphere, are usually the season of maximum prevalence.

Rarely, if ever, do epidemics have their onset before warm weather, and while there are numerous exceptions they ordinarily disappear with cold weather. This is true, even though they may have started late

in the season, or have spread to areas where it is doubtful if the susceptible material could have been exhausted.

This seasonal incidence was first pointed out by Sinkler in 1875 (S44). He observed 86 cases in Philadelphia during a period of 4 years. The seasonal distribution of 44 of these was:

|             |             |            |             |             |             |              |             |             |             |
|-------------|-------------|------------|-------------|-------------|-------------|--------------|-------------|-------------|-------------|
| <i>Mch.</i> | <i>Apr.</i> | <i>May</i> | <i>June</i> | <i>July</i> | <i>Aug.</i> | <i>Sept.</i> | <i>Oct.</i> | <i>Nov.</i> | <i>Dec.</i> |
| 2           | 1           | 1          | 8           | 11          | 9           | 6            | 5           | 0           | 1           |

In 12 instances it was stated merely that the child became ill in the summer; in one instance in the fall; and in the remainder the date of onset was not given.

TABLE 14

REPORTED MORBIDITY AND MORTALITY BY MONTHS IN THE REGISTRATION AREA OF THE UNITED STATES FOR 1921, WITH CASE FATALITY FOR EACH MONTH\*

|                    | JANUARY | FEBRUARY | MARCH | APRIL | MAY | JUNE | JULY | AUGUST | SEPTEMBER | OCTOBER | NOVEMBER | DECEMBER | TOTAL |
|--------------------|---------|----------|-------|-------|-----|------|------|--------|-----------|---------|----------|----------|-------|
| Morbidity.....     | 70      | 65       | 66    | 67    | 64  | 219  | 733  | 1,521  | 1,766     | 1,162   | 323      | 163      | 6,219 |
| Mortality.....     | 49      | 42       | 55    | 40    | 36  | 40   | 161  | 314    | 434       | 273     | 127      | 74       | 1,645 |
| Case fatality..... | 70      | 65       | 83    | 60    | 56  | 18   | 22   | 21     | 25        | 23      | 39       | 45       | 26.4  |

\* Aycock and Eaton, *Am. J. Hyg.*, 4: 682, 1924.

**Seasonal Expectancy on the Part of Physicians.** Aycock and Eaton (A 41) believe that the seasonal incidence of poliomyelitis is probably accentuated by a seasonal expectancy on the part of physicians, and that, although predominantly a summer disease, it prevails to a greater extent in the period from December to May than is shown by the reported cases. They argue this from the higher case fatality during the winter and spring which they found in certain instances. They give as illustration the figures for the United States as a whole for the year 1921, taken from the United States Public Health Reports. In Table 14 are given the morbidity and registered mortality by months in the registration area of the United States for 1921. The case fatality by months, computed from the morbidity and mortality reports, is noticeably higher in the months of fewest cases.

Since clinicians with a wide experience with the disease have not noted



any marked variation in its severity from month to month, the authors concluded that the variation was due to incomplete reporting.

**Secondary Increase in Early Spring.** Aycock and Eaton (A 40) have called attention to the frequent occurrence of a small but definite secondary increase in poliomyelitis occurring in the early spring. This increase, while quantitatively unimportant, may have a significant bearing on the mode of transmission. They have studied the case incidence of poliomyelitis in the United States for the years 1912–1922, the figures being taken largely from the United States Public Health Reports. The total cases for these 11 years was, by months:

| Jan. | Feb. | Mch. | Apr. | May | June  | July  | Aug.   | Sept.  | Oct.  | Nov.  | Dec.  | Total  |
|------|------|------|------|-----|-------|-------|--------|--------|-------|-------|-------|--------|
| 992  | 781  | 957  | 836  | 820 | 1,673 | 8,724 | 15,847 | 12,411 | 7,272 | 2,699 | 1,226 | 54,238 |

This spring increase is shown more plainly by the mortality than the morbidity figures, a fact which the authors believe due to a failure on the part of physicians to recognize the milder forms of the disease in its “off season” and perhaps to a lesser extent to delayed reporting of cases as against prompt reporting of deaths.

**Seasonal Distribution in Endemic and Epidemic Incidence.** Under *Geographic Distribution*, we have commented upon the fact that the incidence of poliomyelitis in more Northern areas is dominated by a few epidemic years. This is true of the seasonal incidence also. Moreover, in estimating this distribution of poliomyelitis, we notice that the large epidemics do not necessarily follow the more expected seasonal distribution for that locality. In the 1916 epidemic in New York City, for example, the peak was the first week in August, the total figures for the State also being highest in August. The “estimated expectancy,” or endemic incidence in New York State is highest in September. A number of workers have met this obvious difficulty by omitting the figures for 1916 in estimating the seasonal incidence. When, however, we consider that in the 1931 epidemic, in the same area, the seasonal distribution was almost identical with that of 1916 (the peak weeks in the City were the same) such an omission does not seem warranted.

In Tables 15 and 16 are given the cases by months for the States of New York and Mississippi, taken from the Public Health Reports for each year for the period 1915–1929, with the mean and median number of cases for each month. These two states are chosen, merely as being representative, in monthly percentage distribution of cases, and in

endemic and epidemic prevalence, of a typical Northern and Southern state.

We have similarly tabulated the cases for each state for the 1915–1929 period. Since space does not permit the inclusion of these tables, we have summarized them in Table 17. In this we give the total cases by months for these years; and the mean and median cases. Since not all

TABLE 15  
POLIOMYELITIS, CASES BY MONTHS, NEW YORK STATE, 1915–1929\*

| YEAR                            | JANUARY | FEBRUARY | MARCH | APRIL | MAY | JUNE | JULY  | AUGUST | SEPTEMBER | OCTOBER | NOVEMBER | DECEMBER | RATE PER<br>100,000 |
|---------------------------------|---------|----------|-------|-------|-----|------|-------|--------|-----------|---------|----------|----------|---------------------|
| 1915                            | 8       | 8        | 5     | 11    | 4   | 10   | 13    | 47     | 50        | 67      | 29       | 5        | 2.6                 |
| 1916                            | 10      | 6        | 5     | 9     | 16  | 345  | 4,054 | 5,773  | 2,201     | 643     | 122      | 39       | 128.7               |
| 1917                            | 16      | 7        | 18    | 18    | 17  | 41   | 44    | 59     | 39        | 15      | 15       | 6        | 2.8                 |
| 1918                            | 4       | 5        | 10    | 13    | 4   | 19   | 38    | 46     | 70        | 16      | 4        | 4        | 2.2                 |
| 1919                            | 4       | 0        | 4     | 6     | 7   | 9    | 4     | 33     | 31        | 20      | 21       | 7        | 1.4                 |
| 1920                            | 2       | 3        | 8     | 2     | 2   | 4    | 14    | 14     | 40        | 69      | 41       | 15       | 2.0                 |
| 1921                            | 9       | 10       | 1     | 8     | 1   | 14   | 68    | 253    | 426       | 262     | 70       | 27       | 11.0                |
| 1922                            | 8       | 5        | 13    | 8     | 15  | 4    | 18    | 101    | 181       | 157     | 67       | 33       | 6.0                 |
| 1923                            | 18      | 7        | 9     | 2     | 17  | 24   | 127   | 231    | 195       | 197     | 75       | 41       | 9.0                 |
| 1924                            | 12      | 11       | 7     | 7     | 8   | 20   | 88    | 353    | 333       | 214     | 114      | 43       | 11.0                |
| 1925                            | 16      | 8        | 9     | 10    | 7   | 21   | 118   | 197    | 195       | 132     | 49       | 28       | 7.0                 |
| 1926                            | 15      | 12       | 21    | 8     | 6   | 13   | 53    | 183    | 198       | 99      | 40       | 26       | 6.0                 |
| 1927                            | 14      | 5        | 4     | 12    | 8   | 10   | 35    | 238    | 309       | 169     | 79       | 33       | 8.0                 |
| 1928                            | 26      | 12       | 16    | 4     | 12  | 16   | 64    | 361    | 328       | 120     | 44       | 18       | 9.0                 |
| 1929                            | 13      | 10       | 3     | 9     | 5   | 8    | 39    | 110    | 161       | 99      | 28       | 10       | 4.0                 |
| Total for 15<br>years . . . . . | 175     | 109      | 133   | 127   | 129 | 558  | 4,777 | 7,999  | 4,757     | 2,279   | 798      | 335      | —                   |
| Mean . . . . .                  | 11.7    | 7.3      | 8.9   | 8.5   | 8.6 | 37.2 | 318.4 | 533.2  | 317.1     | 151.9   | 53.2     | 22.3     | 14.0                |
| Median . . . . .                | 11.7    | 7.3      | 8.0   | 8.3   | 7.3 | 14.3 | 45.3  | 163.3  | 190.3     | 117.0   | 44.7     | 23.6     | 6.3                 |

\* United States Public Health Reports, The Notifiable Diseases, Prevalence in States, 1915–1929.

states have reports for every year we have given the number of years which the totaled figures represent. The median cases correspond (except that more years are included), to the “monthly estimated expectancy” of the Public Health Reports.

**Monthly Percentage Distribution Varies with Latitude.** Aycock (A 36) pointed out that not only is the incidence of poliomyelitis lower in



the Southern part of the United States than in the Northern, but that there is a marked difference in the percentage distribution of cases throughout the year. They have shown in Chart VI the “seasonal fluctuation in the occurrence of poliomyelitis in Northern, Intermediate and Southern states as well as in Australia and New Zealand. In order that the seasonal fluctuation of the disease may be compared in these

TABLE 16  
POLIOMYELITIS, CASES BY MONTHS, MISSISSIPPI, 1915-1929\*

| YEAR                    | JANUARY | FEBRUARY | MARCH | APRIL | MAY | JUNE | JULY | AUGUST | SEPTEMBER | OCTOBER | NOVEMBER | DECEMBER | RATE PER 100,000 |
|-------------------------|---------|----------|-------|-------|-----|------|------|--------|-----------|---------|----------|----------|------------------|
| 1915                    | 4       | 1        | 0     | 0     | 0   | 0    | 0    | 4      | 4         | 3       | 5        | 3        | 4.4              |
| 1916                    | 4       | 11       | 6     | 15    | 36  | 57   | 59   | 31     | 14        | 10      | 8        | 18       | 13.8             |
| 1917                    | 7       | 3        | 2     | 0     | 5   | 9    | 7    | 5      | 1         | 4       | 7        | 6        | 2.8              |
| 1918                    | 3       | 2        | 5     | 2     | 3   | 3    | 12   | 2      | 5         | 6       | 11       | 3        | 2.8              |
| 1919                    | 17      | 7        | 1     | 1     | 1   | 2    | 1    | 10     | 10        | 9       | 8        | 9        | 4.2              |
| 1920                    | 10      | 17       | 7     | 9     | 4   | 0    | 3    | 4      | 5         | 4       | 3        | 0        | 4.0              |
| 1921                    | 5       | 2        | 2     | 12    | 6   | 2    | 6    | 1      | 3         | 4       | 6        | 0        | 3.0              |
| 1922                    | 0       | 1        | 1     | 1     | 2   | 3    | 4    | 0      | 3         | 0       | 6        | 0        | 1.0              |
| 1923                    | 4       | 4        | 2     | 5     | 4   | 5    | 4    | 1      | 3         | 7       | 3        | 1        | 2.0              |
| 1924                    | 1       | 1        | 0     | 0     | 3   | 4    | 2    | 5      | 0         | 4       | 0        | 5        | 1.0              |
| 1925                    | 1       | 4        | 2     | 3     | 4   | 2    | 4    | 8      | 7         | 6       | 3        | 3        | 3.0              |
| 1926                    | 3       | 1        | 1     | 2     | 1   | 6    | 10   | 8      | 6         | 4       | 4        | 3        | 3.0              |
| 1927                    | 1       | 0        | 4     | 3     | 4   | 6    | 2    | 8      | 8         | 6       | 8        | 6        | 3.0              |
| 1928                    | 2       | 4        | 7     | 2     | 3   | 5    | 16   | 7      | 9         | 3       | 0        | 1        | 3.0              |
| 1929                    | 2       | 3        | 1     | 3     | 2   | 3    | 6    | 4      | 2         | 0       | 1        | 1        | 1.4              |
| Total for 15 years..... | 64      | 61       | 41    | 58    | 78  | 107  | 136  | 98     | 80        | 70      | 73       | 59       | —                |
| Mean.....               | 4.3     | 4.1      | 2.7   | 3.9   | 5.2 | 7.1  | 9.1  | 6.5    | 5.3       | 4.7     | 4.9      | 3.9      | 3.5              |
| Median.....             | 3.3     | 2.7      | 2.0   | 2.3   | 3.3 | 3.3  | 4.7  | 4.7    | 4.7       | 4.0     | 5.0      | 3.0      | 3.0              |

\* United States Public Health Reports, The Notifiable Diseases, Prevalence in States, 1915-1929.

different areas, in which, as has already been shown, the incidence of the disease varies markedly, the percentages of the total cases in the year which occurred in each month are plotted. These curves are, therefore, comparable only in so far as seasonal fluctuation is concerned. It will be noted that the most marked seasonal fluctuation in the occurrence of poliomyelitis takes place in the Northern United States and in Australia

and New Zealand, the latter curve being almost exactly the reverse of that for the Northern United States with its peak in February and March, the season in the Southern hemisphere which corresponds to August and September in the Northern hemisphere. It is further shown that the disease tends to occur more evenly throughout the year in the

CHART VI  
POLIOMYELITIS  
SEASONAL DISTRIBUTION

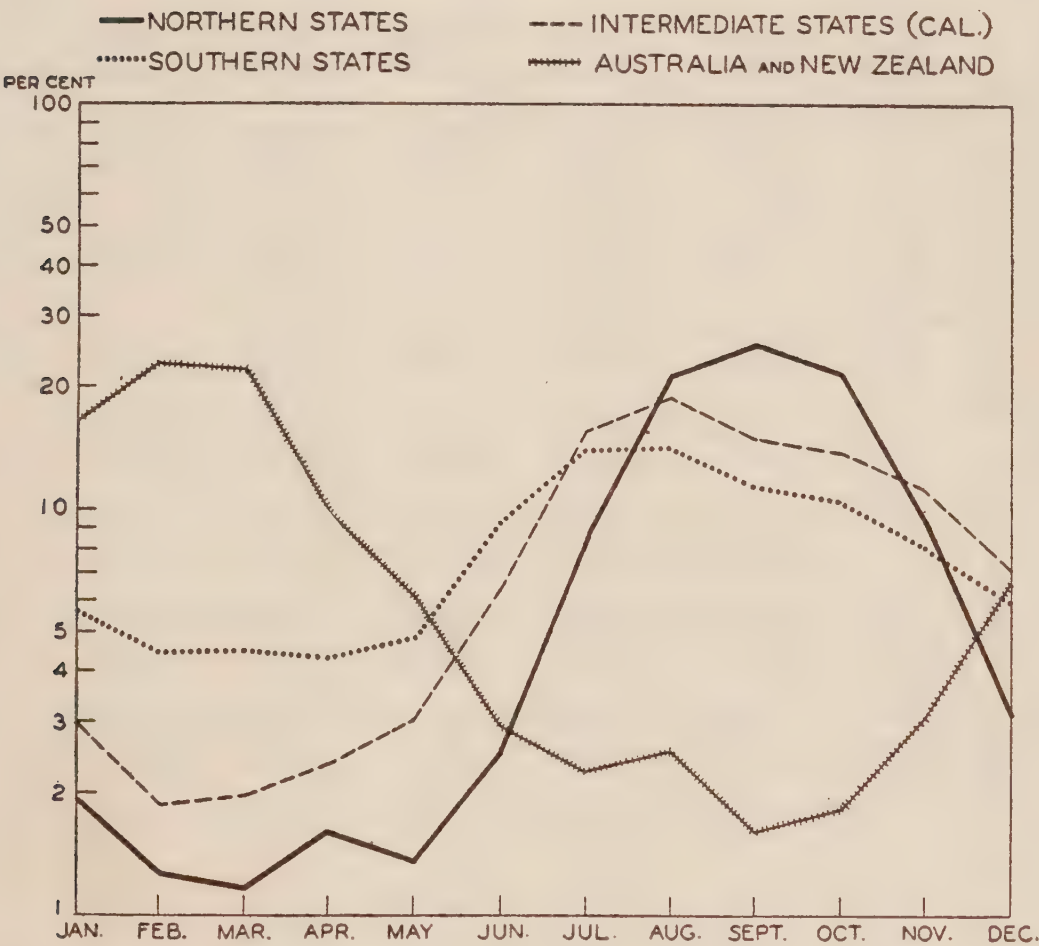


CHART VI. Seasonal distribution of poliomyelitis in different climates: Northern and Southern States, 1912-1927; California, 1913-1927; Australia and New Zealand, June, 1924, to August, 1927. (From Aycock, J. Prev. Med. 3: 245, 1929.)

Southern United States." Table 18, giving the percentage monthly distribution of cases, has been computed from Table 17. It illustrates the concentration of cases in a few summer and fall months in the Northern group, and the more even distribution in the Southern group.

We have followed in Table 18, the idea of Aycock in considering



TABLE 17  
POLIOMYELITIS, TOTAL CASES, MEAN AND MEDIAN NUMBER OF CASES, BY MONTHS, FOR EACH STATE, 1915-1929, AND THE MEAN AND MEDIAN CASE RATE PER 100,000 FOR THOSE YEARS\*

| STATE                         | JANU-<br>ARY | FEBRU-<br>ARY | MARCH | APRIL | MAY  | JUNE | JULY | AUGUST | SEP-<br>TEMBER | OCTO-<br>BER | NOVEM-<br>BER | DECEM-<br>BER | RATE<br>PER<br>100,000 |
|-------------------------------|--------------|---------------|-------|-------|------|------|------|--------|----------------|--------------|---------------|---------------|------------------------|
| Alabama:                      |              |               |       |       |      |      |      |        |                |              |               |               |                        |
| Total cases for 13 years..... | 17           | 21            | 22    | 24    | 33   | 59   | 140  | 127    | 73             | 53           | 33            | 28            | —                      |
| Mean.....                     | 1.3          | 1.6           | 1.7   | 1.8   | 2.5  | 4.5  | 10.8 | 9.8    | 5.6            | 4.1          | 2.5           | 2.1           | 1.9                    |
| Median.....                   | 1.3          | 1.0           | 1.7   | 1.7   | 2.3  | 3.7  | 5.0  | 4.0    | 3.3            | 3.3          | 2.7           | 2.0           | 1.2                    |
| Arizona:                      |              |               |       |       |      |      |      |        |                |              |               |               |                        |
| Total cases for 8 years.....  | 3            | 2             | 2     | 3     | 6    | 20   | 20   | 21     | 23             | 25           | 9             | 3             | —                      |
| Mean.....                     | 0.4          | 0.3           | 0.3   | 0.4   | 0.7  | 2.5  | 2.5  | 2.5    | 2.9            | 2.9          | 1.1           | 0.4           | 3.6                    |
| Median.....                   | 0            | 0             | 0     | 0     | 0    | 0    | 1.0  | 1.0    | 1.0            | 1.0          | 1.0           | 0             | 1.4                    |
| Arkansas:                     |              |               |       |       |      |      |      |        |                |              |               |               |                        |
| Total cases for 7 years.....  | 3            | 5             | 3     | 0     | 1    | 19   | 16   | 28     | 25             | 29           | 13            | 3             | —                      |
| Mean.....                     | 0.4          | 0.7           | 0.4   | 0     | 0.1  | 2.7  | 2.3  | 4.0    | 3.6            | 4.1          | 1.9           | 0.4           | 1.2                    |
| Median.....                   | 0            | 0.3           | 0.3   | 0     | 0    | 1.7  | 2.0  | 2.7    | 3.0            | 2.0          | 0             | 0             | 0.9                    |
| California:                   |              |               |       |       |      |      |      |        |                |              |               |               |                        |
| Total cases for 15 years..... | 138          | 128           | 89    | 100   | 152  | 270  | 552  | 732    | 621            | 513          | 426           | 256           | —                      |
| Mean.....                     | 9.2          | 8.5           | 5.9   | 6.7   | 10.1 | 18.0 | 36.8 | 48.8   | 41.4           | 34.2         | 28.4          | 17.1          | 6.6                    |
| Median.....                   | 7.7          | 3.3           | 4.7   | 3.7   | 6.0  | 6.7  | 10.0 | 16.0   | 18.3           | 16.0         | 16.0          | 11.3          | 3.9                    |
| Colorado:                     |              |               |       |       |      |      |      |        |                |              |               |               |                        |
| Total cases for 10 years..... | 10           | 4             | 8     | 3     | 5    | 5    | 18   | 30     | 39             | 34           | 16            | 7             | —                      |
| Mean.....                     | 1.0          | 0.4           | 0.8   | 0.3   | 0.5  | 0.5  | 1.8  | 3.0    | 3.9            | 3.4          | 1.6           | 0.7           | 1.6                    |
| Median.....                   | 0            | 0             | 1.0   | 0     | 0    | 0    | 0    | 2.0    | 2.5            | 1.5          | 1.5           | 0.5           | 1.0                    |
| Connecticut:                  |              |               |       |       |      |      |      |        |                |              |               |               |                        |
| Total cases for 15 years..... | 27           | 22            | 18    | 24    | 18   | 28   | 229  | 570    | 499            | 263          | 100           | 42            | —                      |
| Mean.....                     | 1.8          | 1.5           | 1.2   | 1.6   | 1.2  | 1.9  | 15.3 | 38.0   | 33.3           | 17.5         | 6.7           | 2.8           | 8.9                    |
| Median.....                   | 1.3          | 1.0           | 1.3   | 1.0   | 1.0  | 1.0  | 3.0  | 11.7   | 12.3           | 10.7         | 4.0           | 2.0           | 3.3                    |

|                               |     |     |     |     |     |      |      |      |      |      |      |      |
|-------------------------------|-----|-----|-----|-----|-----|------|------|------|------|------|------|------|
| Delaware:                     |     |     |     |     |     |      |      |      |      |      |      |      |
| Total cases for 8 years.....  | 1   | 1   | 2   | 0   | 2   | 4    | 6    | 9    | 7    | 5    | 4    | 2    |
| Mean.....                     | 0.1 | 0.1 | 0.3 | 0   | 0.3 | 0.5  | 0.7  | 1.1  | 0.9  | 0.6  | 0.5  | 0.3  |
| Median.....                   | 0   | 0   | 0   | 0   | 0   | 0    | 1.0  | 0    | 1.0  | 0    | 0    | 0    |
| District of Columbia:         |     |     |     |     |     |      |      |      |      |      |      |      |
| Total cases for 15 years..... | 1   | 0   | 6   | 4   | 5   | 3    | 34   | 52   | 54   | 59   | 14   | 6    |
| Mean.....                     | 0.1 | 0   | 0.4 | 0.3 | 0.3 | 0.2  | 2.3  | 3.5  | 3.6  | 3.9  | 0.9  | 0.4  |
| Median.....                   | 0   | 0   | 0   | 0   | 0   | 0    | 0    | 1.7  | 2.3  | 3.3  | 0    | 0    |
| Florida:                      |     |     |     |     |     |      |      |      |      |      |      |      |
| Total cases for 12 years..... | 6   | 9   | 11  | 29  | 22  | 21   | 31   | 37   | 18   | 15   | 16   | 18   |
| Mean.....                     | 0.5 | 0.7 | 0.9 | 2.4 | 1.8 | 1.7  | 2.6  | 3.1  | 1.5  | 1.3  | 1.3  | 1.5  |
| Median.....                   | 0   | 1.0 | 0.5 | 1.0 | 1.0 | 1.0  | 1.0  | 1.5  | 1.0  | 1.0  | 1.0  | 1.0  |
| Georgia:                      |     |     |     |     |     |      |      |      |      |      |      |      |
| Total cases for 8 years.....  | 6   | 10  | 4   | 7   | 6   | 9    | 19   | 9    | 17   | 18   | 21   | 13   |
| Mean.....                     | 0.7 | 1.3 | 0.5 | 0.9 | 0.7 | 1.1  | 2.4  | 1.1  | 2.1  | 2.2  | 2.6  | 1.6  |
| Median.....                   | 0.5 | 1.0 | 0   | 0.5 | 1.0 | 1.0  | 2.0  | 1.0  | 2.5  | 2.0  | 2.5  | 1.5  |
| Idaho:                        |     |     |     |     |     |      |      |      |      |      |      |      |
| Total cases for 7 years.....  | 1   | 3   | 2   | 4   | 4   | 3    | 6    | 21   | 36   | 54   | 25   | 8    |
| Mean.....                     | 0.1 | 0.4 | 0.3 | 0.6 | 0.6 | 0.4  | 0.8  | 3.0  | 5.1  | 7.7  | 3.6  | 1.1  |
| Median.....                   | 0   | 0   | 0   | 0   | 0.3 | 0.3  | 1.0  | 1.0  | 3.3  | 6.3  | 0    | 0.3  |
| Illinois:                     |     |     |     |     |     |      |      |      |      |      |      |      |
| Total cases for 13 years..... | 89  | 75  | 88  | 79  | 91  | 111  | 341  | 655  | 1187 | 871  | 344  | 119  |
| Mean.....                     | 6.8 | 5.8 | 6.8 | 6.1 | 7.0 | 8.5  | 26.2 | 50.4 | 91.3 | 67.0 | 26.5 | 9.1  |
| Median.....                   | 7.0 | 5.3 | 6.7 | 3.3 | 5.3 | 6.0  | 15.0 | 42.7 | 62.7 | 45.3 | 15.7 | 10.0 |
| Indiana:                      |     |     |     |     |     |      |      |      |      |      |      |      |
| Total cases for 14 years..... | 30  | 26  | 20  | 15  | 13  | 30   | 69   | 147  | 210  | 226  | 107  | 40   |
| Mean.....                     | 2.1 | 1.9 | 1.4 | 1.1 | 0.9 | 2.1  | 4.9  | 10.5 | 15.0 | 16.1 | 7.6  | 2.9  |
| Median.....                   | 1.0 | 1.0 | 1.0 | 0.5 | 1.0 | 1.5  | 1.5  | 9.0  | 7.5  | 11.0 | 4.0  | 2.5  |
| Iowa:                         |     |     |     |     |     |      |      |      |      |      |      |      |
| Total cases for 13 years..... | 21  | 21  | 15  | 15  | 13  | 23.6 | 136  | 245  | 411  | 265  | 102  | 46   |
| Mean.....                     | 1.6 | 1.6 | 1.1 | 1.1 | 1.0 | 1.8  | 10.5 | 18.8 | 31.6 | 20.4 | 7.8  | 3.5  |
| Median.....                   | 1.3 | 1.7 | 0.7 | 0.3 | 1.0 | 0.7  | 1.7  | 7.0  | 21.0 | 20.3 | 5.7  | 3.0  |

\* United States Public Health Reports, The Notifiable Diseases, Prevalence in States, 1915-1929.



TABLE 17—Continued

| STATE                         | JANU-<br>ARY | FEBRU-<br>ARY | MARCH | APRIL | MAY | JUNE | JULY | AUGUST | SEP-<br>TEMBER | OCTO-<br>BER | NOVEM-<br>BER | DECEM-<br>BER | RATE<br>PER<br>100,000 |
|-------------------------------|--------------|---------------|-------|-------|-----|------|------|--------|----------------|--------------|---------------|---------------|------------------------|
| Kansas:                       |              |               |       |       |     |      |      |        |                |              |               |               |                        |
| Total cases for 13 years..... | 22           | 14            | 22    | 12    | 18  | 42   | 84   | 243    | 265            | 169          | 61            | 37            | —                      |
| Mean.....                     | 1.7          | 1.1           | 1.7   | 0.9   | 1.4 | 3.2  | 6.5  | 18.7   | 20.4           | 13.0         | 4.7           | 2.8           | 4.2                    |
| Median.....                   | 2.0          | 1.0           | 1.3   | 0.6   | 1.0 | 1.6  | 5.6  | 12.3   | 18.0           | 9.0          | 5.0           | 2.3           | 3.6                    |
| Kentucky: (Not given)         |              |               |       |       |     |      |      |        |                |              |               |               |                        |
| Louisiana:                    |              |               |       |       |     |      |      |        |                |              |               |               |                        |
| Total cases for 14 years..... | 20           | 20            | 20    | 22    | 28  | 41   | 75   | 45     | 64             | 34           | 34            | 23            | —                      |
| Mean.....                     | 1.4          | 1.4           | 1.4   | 1.6   | 2.0 | 2.9  | 5.3  | 3.2    | 4.6            | 2.4          | 2.4           | 1.6           | 1.7                    |
| Median.....                   | 1.0          | 1.0           | 1.5   | 1.0   | 1.5 | 2.0  | 2.5  | 3.0    | 4.0            | 2.5          | 2.0           | 2.0           | 1.4                    |
| Maine:                        |              |               |       |       |     |      |      |        |                |              |               |               |                        |
| Total cases for 14 years..... | 22           | 8             | 9     | 9     | 12  | 10   | 21   | 86     | 175            | 174          | 95            | 31            | —                      |
| Mean.....                     | 1.6          | 0.6           | 0.6   | 0.6   | 0.9 | 0.7  | 1.5  | 6.1    | 12.5           | 12.4         | 6.8           | 2.2           | 5.9                    |
| Median.....                   | 1.0          | 0             | 0.5   | 0     | 0.5 | 0    | 0.5  | 2.0    | 3.0            | 3.0          | 3.0           | 1.0           | 3.0                    |
| Maryland:                     |              |               |       |       |     |      |      |        |                |              |               |               |                        |
| Total cases for 15 years..... | 31           | 19            | 15    | 22    | 32  | 49   | 160  | 420    | 442            | 326          | 120           | 35            | —                      |
| Mean.....                     | 2.1          | 1.3           | 1.0   | 1.5   | 2.1 | 3.3  | 10.7 | 28.0   | 29.5           | 21.7         | 8.0           | 2.3           | 7.2                    |
| Median.....                   | 2.0          | 1.0           | 1.0   | 1.0   | 2.0 | 2.3  | 10.0 | 16.3   | 15.0           | 11.0         | 6.0           | 1.7           | 4.8                    |
| Massachusetts:                |              |               |       |       |     |      |      |        |                |              |               |               |                        |
| Total cases for 14 years..... | 115          | 69            | 72    | 61    | 61  | 85   | 323  | 1049   | 1800           | 1600         | 596           | 234           | —                      |
| Mean.....                     | 8.2          | 4.9           | 5.1   | 4.3   | 4.3 | 6.1  | 23.1 | 74.9   | 128.6          | 114.3        | 42.6          | 16.7          | 11.4                   |
| Median.....                   | 7.0          | 4.0           | 5.0   | 4.0   | 4.5 | 5.0  | 18.5 | 46.5   | 56.5           | 31.0         | 20.0          | 10.0          | 6.0                    |
| Michigan:                     |              |               |       |       |     |      |      |        |                |              |               |               |                        |
| Total cases for 15 years..... | 51           | 45            | 49    | 30    | 36  | 70   | 205  | 571    | 968            | 624          | 242           | 94            | —                      |
| Mean.....                     | 3.4          | 3.0           | 3.3   | 2.0   | 2.4 | 4.7  | 13.7 | 38.1   | 64.5           | 41.6         | 16.1          | 6.3           | 5.3                    |
| Median.....                   | 2.7          | 2.7           | 3.0   | 2.0   | 2.7 | 3.0  | 6.7  | 17.0   | 26.3           | 21.0         | 8.3           | 4.0           | 2.6                    |
| Minnesota:                    |              |               |       |       |     |      |      |        |                |              |               |               |                        |
| Total cases for 15 years..... | 28           | 19            | 32    | 31    | 41  | 126  | 598  | 1119   | 960            | 535          | 164           | 67            | —                      |
| Mean.....                     | 1.9          | 1.3           | 2.1   | 2.1   | 2.7 | 8.4  | 39.8 | 74.6   | 64.0           | 35.7         | 10.9          | 4.5           | 10.1                   |
| Median.....                   | 2.0          | 1.0           | 1.3   | 1.3   | 2.3 | 3.7  | 10.0 | 21.7   | 22.3           | 20.0         | 11.0          | 3.7           | 4.0                    |

|                               |     |     |     |     |     |     |      |       |      |      |      |     |      |
|-------------------------------|-----|-----|-----|-----|-----|-----|------|-------|------|------|------|-----|------|
| Mississippi:                  | 64  | 61  | 41  | 58  | 78  | 107 | 136  | 98    | 80   | 70   | 73   | 59  | —    |
| Total cases for 15 years..... |     |     |     |     |     |     |      |       |      |      |      |     |      |
| Mean.....                     | 4.3 | 4.7 | 2.7 | 3.9 | 5.2 | 7.1 | 9.1  | 6.5   | 5.3  | 4.7  | 4.9  | 3.9 | 3.5  |
| Median.....                   | 3.3 | 2.7 | 2.0 | 2.3 | 3.3 | 3.3 | 4.7  | 4.7   | 4.7  | 4.0  | 5.0  | 3.0 | 3.0  |
| Missouri:                     |     |     |     |     |     |     |      |       |      |      |      |     |      |
| Total cases for 6 years.....  | 10  | 6   | 11  | 7   | 6   | 5   | 23   | 105   | 140  | 136  | 56   | 23  | —    |
| Mean.....                     | 1.7 | 1.0 | 1.8 | 1.2 | 1.0 | 0.8 | 3.8  | 17.5  | 23.3 | 22.7 | 9.3  | 3.8 | 2.7  |
| Median.....                   | 1.0 | 0.5 | 1.5 | 1.0 | 0   | 0.5 | 2.5  | 7.5   | 10.5 | 10.5 | 4.5  | 4.0 | 1.5  |
| Montana:                      |     |     |     |     |     |     |      |       |      |      |      |     |      |
| Total cases for 14 years..... | 4   | 7   | 5   | 12  | 7   | 15  | 42   | 186   | 158  | 92   | 44   | 20  | —    |
| Mean.....                     | 0.3 | 0.5 | 0.3 | 0.9 | 0.5 | 1.1 | 3.0  | 13.2  | 11.3 | 6.6  | 3.1  | 1.4 | 7.5  |
| Median.....                   | 0   | 0   | 0   | 0   | 0   | 1.0 | 2.5  | 4.5   | 5.5  | 4.0  | 2.0  | 0.5 | 4.5  |
| Nebraska:                     |     |     |     |     |     |     |      |       |      |      |      |     |      |
| Total cases for 12 years..... | 6   | 8   | 14  | 8   | 5   | 10  | 26   | 95    | 141  | 170  | 69   | 24  | —    |
| Mean.....                     | 0.5 | 0.7 | 1.2 | 0.7 | 0.4 | 0.8 | 2.2  | 7.9   | 11.7 | 14.2 | 5.7  | 2.0 | 3.5  |
| Median.....                   | 0   | 0   | 1.0 | 1.0 | 0   | 0   | 1.0  | 4.5   | 7.5  | 6.0  | 3.0  | 1.5 | 2.3  |
| Nevada:                       |     |     |     |     |     |     |      |       |      |      |      |     |      |
| Total cases for 5 years.....  | 12  | 1   | 0   | 1   | 4   | 9   | 1    | 3     | 2    | 12   | 2    | 4   | —    |
| Mean.....                     | 2.4 | 0.2 | 0   | 0.2 | 0.8 | 1.8 | 0.2  | 0.6   | 0.4  | 2.4  | 0.4  | 0.8 | 13.2 |
| Median.....                   | 0.7 | 0   | 0   | 0   | 0.7 | 0   | 0    | 0     | 0    | 0.3  | 0    | 0.7 | 9.7  |
| New Hampshire:                |     |     |     |     |     |     |      |       |      |      |      |     |      |
| Total cases for 10 years..... | 3   | 5   | 2   | 8   | 2   | 5   | 9    | 30    | 48   | 61   | 14   | 6   | —    |
| Mean.....                     | 0.3 | 0.5 | 0.2 | 0.8 | 0.2 | 0.5 | 0.9  | 3.0   | 4.8  | 6.1  | 1.4  | 0.6 | 4.4  |
| Median.....                   | 0   | 0   | 0   | 1.0 | 0   | 0   | 0.5  | 2.0   | 3.5  | 2.5  | 0    | 0   | 3.5  |
| New Jersey:                   |     |     |     |     |     |     |      |       |      |      |      |     |      |
| Total cases for 15 years..... | 43  | 24  | 53  | 40  | 51  | 70  | 797  | 2454  | 1352 | 494  | 155  | 66  | —    |
| Mean.....                     | 2.9 | 1.6 | 3.5 | 2.7 | 3.4 | 4.7 | 53.1 | 163.6 | 90.1 | 42.9 | 10.3 | 4.4 | 12.1 |
| Median.....                   | 2.6 | 1.3 | 3.0 | 2.7 | 2.3 | 3.3 | 8.0  | 17.7  | 15.0 | 11.3 | 6.0  | 3.7 | 2.3  |
| New Mexico:                   |     |     |     |     |     |     |      |       |      |      |      |     |      |
| Total cases for 10 years..... | 6   | 8   | 3   | 4   | 1   | 4   | 67   | 45    | 50   | 52   | 20   | 8   | —    |
| Mean.....                     | 0.6 | 0.8 | 0.3 | 0.4 | 0.1 | 0.4 | 6.7  | 4.5   | 5.0  | 5.2  | 2.0  | 0.8 | 7.0  |
| Median.....                   | 0   | 0   | 0   | 0   | 0   | 0   | 0    | 0.5   | 0.5  | 1.5  | 0.5  | 0.5 | 2.0  |



TABLE 17—Continued

| STATE                         | JANU-<br>ARY | FEBRU-<br>ARY | MARCH | APRIL | MAY | JUNE | JULY  | AUGUST | SEP-<br>TEMBER | OCTO-<br>BER | NOVEM-<br>BER | DECEM-<br>BER | RATE<br>PER<br>100,000 |
|-------------------------------|--------------|---------------|-------|-------|-----|------|-------|--------|----------------|--------------|---------------|---------------|------------------------|
| New York:                     |              |               |       |       |     |      |       |        |                |              |               |               |                        |
| Total cases for 15 years..... | 175          | 109           | 133   | 127   | 129 | 558  | 4777  | 7999   | 4757           | 2279         | 798           | 335           | —                      |
| Mean.....                     | 11.7         | 7.3           | 8.9   | 8.5   | 8.6 | 37.2 | 318.4 | 533.2  | 317.1          | 151.9        | 53.2          | 22.3          | 14.0                   |
| Median.....                   | 11.7         | 7.3           | 8.0   | 8.3   | 7.3 | 14.3 | 45.3  | 163.3  | 190.3          | 117.0        | 44.7          | 23.6          | 6.3                    |
| North Carolina:               |              |               |       |       |     |      |       |        |                |              |               |               |                        |
| Total cases for 11 years..... | 15           | 17            | 15    | 14    | 19  | 47   | 119   | 109    | 71             | 67           | 49            | 27            | —                      |
| Mean.....                     | 1.4          | 1.5           | 1.4   | 1.3   | 1.7 | 4.3  | 10.8  | 9.9    | 6.5            | 6.1          | 4.4           | 2.5           | 1.9                    |
| Median.....                   | 1.0          | 1.7           | 1.0   | 1.0   | 1.7 | 2.7  | 4.7   | 5.0    | 5.0            | 3.7          | 3.7           | 2.0           | 1.2                    |
| North Dakota:                 |              |               |       |       |     |      |       |        |                |              |               |               |                        |
| Total cases for 12 years..... | 19           | 14            | 14    | 11    | 10  | 14   | 35    | 148    | 126            | 104          | 74            | 19            | —                      |
| Mean.....                     | 1.6          | 1.2           | 1.2   | 0.9   | 0.8 | 1.2  | 2.9   | 12.3   | 10.5           | 8.7          | 6.2           | 1.6           | 7.2                    |
| Median.....                   | 1.0          | 0             | 0.5   | 0     | 0   | 0.5  | 0     | 5.0    | 3.5            | 3.5          | 4.5           | 0.5           | 4.0                    |
| Ohio:                         |              |               |       |       |     |      |       |        |                |              |               |               |                        |
| Total cases for 15 years..... | 84           | 77            | 60    | 76    | 64  | 107  | 385   | 1031   | 1174           | 781          | 317           | 126           | —                      |
| Mean.....                     | 5.6          | 5.1           | 4.0   | 5.0   | 4.3 | 7.1  | 25.7  | 68.7   | 78.3           | 52.1         | 21.1          | 8.4           | 4.8                    |
| Median.....                   | 4.3          | 5.0           | 3.3   | 4.3   | 3.0 | 4.7  | 17.6  | 47.6   | 45.7           | 38.0         | 10.7          | 6.7           | 3.3                    |
| Oklahoma:                     |              |               |       |       |     |      |       |        |                |              |               |               |                        |
| Total cases for 4 years.....  | 11           | 15            | 7     | 6     | 2   | 13   | 24    | 41     | 47             | 60           | 21            | 18            | —                      |
| Mean.....                     | 2.7          | 3.7           | 1.7   | 1.5   | 0.5 | 3.2  | 6.0   | 10.2   | 11.7           | 15.0         | 5.2           | 4.5           | 3.0                    |
| Median.....                   | 3.0          | 4.0           | 1.0   | 1.0   | 0.5 | 4.0  | 4.0   | 2.5    | 6.0            | 7.5          | 4.5           | 4.5           | 2.0                    |
| Oregon:                       |              |               |       |       |     |      |       |        |                |              |               |               |                        |
| Total cases for 15 years..... | 30           | 18            | 17    | 9     | 3   | 10   | 13    | 59     | 131            | 235          | 168           | 89            | —                      |
| Mean.....                     | 2.0          | 1.2           | 1.1   | 0.6   | 0.2 | 0.7  | 0.9   | 3.9    | 8.7            | 15.7         | 11.2          | 5.9           | 6.0                    |
| Median.....                   | 0            | 0             | 0     | 0     | 0   | 0    | 0     | 0      | 3.7            | 4.7          | 2.0           | 1.0           | 2.4                    |
| Pennsylvania:                 |              |               |       |       |     |      |       |        |                |              |               |               |                        |
| Total cases for 14 years..... | 63           | 64            | 70    | 54    | 51  | 80   | 359   | 1386   | 1622           | 916          | 345           | 132           | —                      |
| Mean.....                     | 4.5          | 4.6           | 5.0   | 3.9   | 3.6 | 5.7  | 25.6  | 99.0   | 115.8          | 65.4         | 24.6          | 9.4           | 4.2                    |
| Median.....                   | 4.0          | 3.5           | 3.0   | 2.5   | 3.0 | 4.0  | 10.0  | 46.0   | 51.0           | 34.5         | 13.0          | 6.0           | 2.0                    |

|                               |     |     |     |     |     |     |      |      |      |      |      |     |
|-------------------------------|-----|-----|-----|-----|-----|-----|------|------|------|------|------|-----|
| Rhode Island:                 |     |     |     |     |     |     |      |      |      |      |      |     |
| Total cases for 13 years..... | 4   | 2   | 4   | 2   | 6   | 13  | 52   | 77   | 74   | 47   | 24   | 11  |
| Mean.....                     | 0.3 | 0.1 | 0.3 | 0.1 | 0.5 | 1.0 | 4.0  | 5.9  | 5.7  | 3.6  | 1.9  | 0.9 |
| Median.....                   | 0   | 0   | 0   | 0   | 0   | 0.3 | 1.0  | 1.7  | 4.7  | 2.7  | 1.0  | 0.3 |
| South Carolina:               |     |     |     |     |     |     |      |      |      |      |      |     |
| Total cases for 9 years.....  | 29  | 29  | 13  | 12  | 24  | 19  | 39   | 82   | 51   | 49   | 26   | 30  |
| Mean.....                     | 3.2 | 3.2 | 1.4 | 1.3 | 2.7 | 2.1 | 4.3  | 9.1  | 5.7  | 5.4  | 2.9  | 3.3 |
| Median.....                   | 0.3 | 2.3 | 0.7 | 0.3 | 2.0 | 1.3 | 1.7  | 1.7  | 3.0  | 3.0  | 1.0  | 0.7 |
| South Dakota:                 |     |     |     |     |     |     |      |      |      |      |      |     |
| Total cases for 12 years..... | 13  | 9   | 11  | 13  | 11  | 10  | 20   | 49   | 74   | 106  | 57   | 18  |
| Mean.....                     | 1.1 | 0.7 | 0.9 | 1.1 | 0.9 | 0.8 | 1.7  | 4.1  | 6.2  | 8.9  | 4.7  | 1.5 |
| Median.....                   | 0.5 | 0.5 | 1.0 | 0.5 | 0.5 | 1.0 | 2.0  | 3.0  | 6.0  | 7.0  | 3.5  | 1.0 |
| Tennessee:                    |     |     |     |     |     |     |      |      |      |      |      |     |
| Total cases for 6 years.....  | 7   | 7   | 7   | 6   | 2   | 20  | 34   | 83   | 68   | 48   | 28   | 17  |
| Mean.....                     | 1.2 | 1.2 | 1.2 | 1.0 | 0.3 | 3.3 | 5.7  | 13.8 | 11.3 | 8.0  | 4.7  | 2.8 |
| Median.....                   | 0.5 | 1.0 | 1.0 | 1.0 | 0   | 2.5 | 2.0  | 10.5 | 11.0 | 4.0  | 1.0  | 2.0 |
| Texas:                        |     |     |     |     |     |     |      |      |      |      |      |     |
| Total cases for 6 years.....  | 18  | 8   | 3   | 5   | 14  | 30  | 46   | 67   | 105  | 51   | 34   | 37  |
| Mean.....                     | 3.0 | 1.3 | 0.5 | 0.8 | 2.3 | 5.0 | 7.7  | 11.2 | 17.5 | 8.5  | 5.7  | 6.2 |
| Median.....                   | 1.5 | 0.5 | 0.5 | 0.5 | 2.5 | 4.0 | 5.5  | 4.5  | 4.0  | 0.5  | 2.5  | 0.5 |
| Vermont:                      |     |     |     |     |     |     |      |      |      |      |      |     |
| Total cases for 14 years..... | 13  | 7   | 19  | 4   | 4   | 55  | 81   | 143  | 148  | 127  | 54   | 12  |
| Mean.....                     | 0.9 | 0.5 | 1.3 | 0.3 | 0.3 | 3.9 | 5.8  | 10.1 | 10.6 | 9.1  | 3.8  | 0.9 |
| Median.....                   | 0   | 0   | 0   | 0   | 0   | 0.5 | 3.0  | 8.5  | 9.5  | 9.5  | 2.5  | 0.5 |
| Virginia:                     |     |     |     |     |     |     |      |      |      |      |      |     |
| Total cases for 15 years..... | 78  | 95  | 99  | 110 | 86  | 132 | 374  | 417  | 341  | 307  | 169  | 71  |
| Mean.....                     | 5.2 | 6.3 | 6.6 | 7.3 | 5.7 | 8.8 | 24.9 | 27.8 | 22.7 | 20.5 | 11.3 | 4.7 |
| Median.....                   | 2.7 | 4.3 | 4.3 | 4.3 | 4.0 | 6.3 | 18.0 | 19.6 | 14.3 | 15.3 | 8.3  | 4.0 |
| Washington:                   |     |     |     |     |     |     |      |      |      |      |      |     |
| Total cases for 14 years..... | 45  | 18  | 19  | 22  | 15  | 15  | 54   | 280  | 561  | 512  | 223  | 91  |
| Mean.....                     | 3.2 | 1.3 | 1.3 | 1.6 | 1.1 | 1.1 | 3.9  | 20.0 | 40.1 | 36.6 | 15.9 | 6.5 |
| Median.....                   | 1.0 | 0.5 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0  | 5.5  | 4.0  | 4.5  | 2.0  | 2.0 |



TABLE 17—*Concluded*

| STATE                         | JANU-<br>ARY | FEBRU-<br>ARY | MARCH | APRIL | MAY | JUNE | JULY | AUGUST | SEP-<br>TEMBER | OCTO-<br>BER | NOVEM-<br>BER | DECEM-<br>BER | RATE<br>PER<br>100,000 |
|-------------------------------|--------------|---------------|-------|-------|-----|------|------|--------|----------------|--------------|---------------|---------------|------------------------|
| West Virginia:                |              |               |       |       |     |      |      |        |                |              |               |               |                        |
| Total cases for 12 years..... | 104          | 23            | 19    | 7     | 19  | 28   | 109  | 247    | 230            | 149          | 79            | 35            | —                      |
| Mean.....                     | 8.6          | 1.9           | 1.6   | 0.6   | 1.6 | 2.3  | 9.1  | 20.6   | 19.2           | 12.4         | 6.6           | 2.9           | 5.7                    |
| Median.....                   | 0.5          | 1.0           | 1.0   | 0     | 1.0 | 2.0  | 6.0  | 11.0   | 7.5            | 3.0          | 3.5           | 1.5           | 2.5                    |
| Wisconsin:                    |              |               |       |       |     |      |      |        |                |              |               |               |                        |
| Total cases for 15 years..... | 36           | 52            | 76    | 61    | 49  | 38   | 258  | 504    | 583            | 333          | 151           | 56            | —                      |
| Mean.....                     | 2.4          | 3.5           | 5.1   | 4.1   | 3.3 | 2.5  | 17.2 | 33.6   | 38.8           | 22.2         | 10.1          | 3.7           | 5.5                    |
| Median.....                   | 2.7          | 2.7           | 2.0   | 2.3   | 2.7 | 2.0  | 5.0  | 11.3   | 15.0           | 13.3         | 6.7           | 3.3           | 2.7                    |
| Wyoming:                      |              |               |       |       |     |      |      |        |                |              |               |               |                        |
| Total cases for 13 years..... | 0            | 0             | 2     | 2     | 4   | 2    | 5    | 18     | 11             | 15           | 5             | 1             | —                      |
| Mean.....                     | 0            | 0             | 0.1   | 0.1   | 0.3 | 0.1  | 0.3  | 1.3    | 0.8            | 1.1          | 0.3           | 0.1           | 2.4                    |
| Median.....                   | 0            | 0             | 0     | 0     | 0   | 0    | 0    | 1.0    | 0.5            | 0            | 0             | 0             | 2.0                    |

separately the seasonal incidence in California, since it differs from both the Southern and Northern types partaking in some respects of each. As is seen in this table the percentage monthly distribution is of the Southern rather than the Northern type. This may be due to the even climate of California, or to the fact that this large state runs north and south. It is sometimes forgotten that its latitude corresponds to the area covered by the states from South Carolina to Massachusetts. It might be that a detailed study of the various sections of the state would show more sharp variation, forming a series of peaks as the season advanced northward, and resulting in a flattened curve for the state as a whole. This was true in 1930 of the 1,707 cases in California, when an

TABLE 18  
PERCENTAGE MONTHLY DISTRIBUTION OF CASES IN NORTHERN AND SOUTHERN STATES, 1915-1929\*

|                 | JANUARY | FEBRUARY | MARCH | APRIL | MAY | JUNE | JULY | AUGUST | SEPTEMBER | OCTOBER | NOVEMBER | DECEMBER |
|-----------------|---------|----------|-------|-------|-----|------|------|--------|-----------|---------|----------|----------|
| Northern†.....  | 1.5     | 1.2      | 1.5   | 1.2   | 1.2 | 2.4  | 6.9  | 31.6   | 26.0      | 17.2    | 7.0      | 2.5      |
| Southern†.....  | 3.3     | 3.9      | 2.6   | 3.5   | 4.8 | 9.1  | 16.5 | 17.8   | 14.1      | 11.4    | 7.2      | 5.6      |
| California..... | 3.5     | 3.3      | 2.2   | 2.6   | 4.0 | 7.1  | 11.8 | 19.0   | 16.1      | 12.7    | 11.0     | 6.6      |

\* Calculated from figures in Table 17.

† As Southern states are classified: North Carolina, South Carolina, Georgia, Florida, Alabama, Tennessee, Mississippi, Louisiana, Arkansas, Oklahoma, Texas, New Mexico and Arizona. All others, except California, included in the Northern group.

August peak represented the cases in and around Los Angeles, and an October peak the San Francisco outbreak.

**The Lag with Latitude.** From Table 17 it will be seen that poliomyelitis in the United States shows a somewhat irregular retardation in season as we proceed North. Thus the month of highest incidence in the group of Gulf States is July; in the Middle Atlantic, August; in New England, September. This phenomenon is shown more regularly in the sections farther North where the incidence is large enough to absorb epidemics which are out of line with the more usual distribution. Since poliomyelitis is more prevalent in the North, the curve for the United States as a whole is dominated by the Northern figures.

These figures represent total cases. In any locality the peak month will vary from year to year. Forsbeck and Luther (F 57) say that in



Massachusetts 1907-1929, the peak has been July, 3 times; August, 6½ times; September, 7½ times; October, 7 times (a tie being given a value of ½). They could detect no relationship between the time of peak and the incidence of the years. They do note, however, a tendency for the peak to occur later in Massachusetts now than formerly: in the first 11 years, the peak occurred in July or August, 6 times, as compared with 5 times for September or October. In the last 12 years, the peak occurred in July or August, 3 times, as compared with 9 times for September or October.

Epidemics may, of course, occur at any time of the year. Levaditi, Schmutz and Willemin (L 51) reported that in the epidemic of 1930 in Alsace the peak was in July. They call attention to the fact that in the Iceland epidemic of 1924 (I 1a), and also in the recent Finland epidemic (Lövegren 1930, L 61 a) the peaks were early.

### Epidemics Occurring in Cold Weather

*Resistance of Virus to Cold.* Flexner and Lewis (F 42) reported that a specimen of cord from a human case had retained its virulence for 40 days at  $-2$  to  $-4^{\circ}$ , and for 50 days at  $+4^{\circ}\text{C}$ . They comment: "These experiments have a bearing on the epidemiology of the disease, and indicate that the reduction in cases which occurs with the onset of cold weather does not depend upon the destruction of the virus, although it may have to do with an effect on its multiplication."

While most epidemics subside with the onset of cold weather, there have been enough exceptions to make it certain that the incidence of poliomyelitis is not necessarily related to temperature. Several of the Canadian outbreaks have lasted well past frost. Thus Hardman and McKay (H 11) show that in Ontario in 1929, while September was the peak month (244 cases), October had 141; November, 53; and December, 12. In Montreal in 1931, the epidemic did not gain headway until September, October being the peak month.

*Winter Epidemics.* Leake, Bolten and Smith (L 20) investigated an outbreak which occurred in Elkins, West Virginia, during December, 1916, and January, 1917. They say in part:

"Particular attention was attracted to the West Virginia epidemic of poliomyelitis because it occurred in the winter. At the time it was thought to be the first winter outbreak in the United States; indeed it was the first to assume anything like epidemic proportions, but a search of the records has revealed other outbreaks in this country during cold weather. Scandinavian observers had called attention to a few winter

outbreaks in Sweden and Norway although no definite study had been made of the temperature conditions. A criterion must be adopted as to what constitutes a winter outbreak; the mere months of the year signify very different weather in different parts of the globe. Further, we know that occasional poliomyelitis occurs practically everywhere and in all seasons; these isolated winter cases, however, are unimportant as regards a study of conditions of infection, for it has been known ever since the epidemiologic study of poliomyelitis began that some cases occur apparently without any relation to each other, just as do cases of non-infectious nervous diseases. Therefore, it is here assumed that to be considered a winter outbreak two or more connected cases must occur after the temperature has remained below freezing for 24 hours. A study of the available literature reveals 38 such outbreaks, not including the West Virginia epidemic. The official meteorological records were studied, Norwegian, Swedish, Austrian, Prussian, Hessian or American, as the case might be, and by interpolation from the surrounding stations, the approximate temperatures of the places where outbreaks occurred could be obtained. Besides mere distance, there had to be taken into consideration altitude, proximity to bodies of water, and direction of mountain ranges. Fortunately there were meteorological stations at several of the places themselves, as at Elkins." (They give here a table of 39 such winter outbreaks.)

"Some of these outbreaks were far north of the Arctic Circle. In some, the thermometer went below freezing nearly every day of the outbreak, and in some it remained below practically the entire time. In 15 of the outbreaks the thermometer went below zero Fahrenheit, the lowest temperature recorded being 29° below zero Fahrenheit—34° below zero Centigrade—at Misvär, Norway. The contagion was apparently of the most direct sort in a few cases, notably in some of a group south of Åtvidaberg, Sweden, and in the Mosjöen epidemic in Norway."

While reported as separate outbreaks in the literature, it is to be observed that most of those outbreaks listed were really parts of two great epidemic waves. Fifteen occurred in the Scandinavian Peninsula as parts of the epidemic of 1904–1906, and 15 in the great epidemic of 1910–1913. One other epidemic in 1886 occurred in Norway. That is to say, 31 of these 39 reported winter outbreaks occurred in Scandinavia, 30 of them in the two great epidemics.



The remaining 8 outbreaks occurred in:

| <i>Locality</i>                              | <i>Date</i>                         | <i>Cases</i> | <i>Author Cited</i>        |
|----------------------------------------------|-------------------------------------|--------------|----------------------------|
| Vienna and Lower Austria                     | November, 1908—February, 1909       | 125          | Zappert                    |
| Marburg and suburbs, Germany                 | November 20—December 3, 1909        | 10           | Müller                     |
| Hager and vicinity, Germany                  | December, 1909                      | 41           | Krause                     |
| Central Nebraska, U. S. A.                   | November—December, 1910             | 20           | McClanahan                 |
| Ware, Mass., U. S. A.                        | December, 1910—January 1, 1911      | 3            | Rosenau, Shepard and Amoss |
| Lansdowne, Pennsylvania, U. S. A.            | November 21—December 14, 1916       | 5            | Le Boutillier              |
| Waterbury, Vermont, U. S. A.                 | March, 1917                         | 5            | Public Health Reports      |
| Elkins and vicinity, West Virginia, U. S. A. | November 22, 1916—February 11, 1917 | 78           | Leake, Bolten and Smith    |

These outbreaks have one point in common: all were extensions into the winter months of extensive summer prevalence. The epidemic in Lower Austria lasted through the summer of 1908 into the winter. Germany in 1909 suffered an extensive epidemic in Westphalia, Rhenish Prussia, Marburg, etc., comprising about 900 cases. In 1910, Nebraska reported about 200 cases; and Massachusetts 845. The Pennsylvania, Vermont and West Virginia outbreaks were subsequent to the great 1916 epidemic involving a large part of the Northeastern United States. We have come across no report in the literature of an isolated outbreak, of any size, which has arisen during the winter months. The usual experience has been the extension into cold weather of epidemics already under way.

*Types of Epidemic Wave.* Curves representing the epidemic wave of poliomyelitis epidemics depend for their abruptness largely upon the extent of the area reported upon. The outbreaks occurring in cities or towns are apt to be abrupt when compared with those reported from larger areas. The latter are, in reality, a series of peaks as the disease spreads outward, and tend to be correspondingly flattened.

Even for cities, the curve representing the epidemic wave is not necessarily of one type only. The New York City epidemic of 1916 showed a curve which had a slightly longer descending than ascending limb and in the 1931 epidemic, the descending limb was even more prolonged. In Winnipeg in 1928, the epidemic curve shows a slightly

longer ascending than descending limb (M 31) but in the Glasgow epidemic of the same year, the ascending limb of the curve was markedly longer (H 4).

*Explanations for the Seasonal Incidence.* No adequate explanation of the seasonal incidence in poliomyelitis has been offered. The various theories may be briefly summarized as attributing it to:

(1) Seasonal modifications of the virus—that the virus may itself wax and wane with season.

(2) Seasonal variations in the host—autarcesis. This theory argues that since the virus is carried only by human beings at a constant temperature, the host, and not the virus, makes the adjustment to season. This is considered under *The Host*.

(3) Seasonal variations in the transmission factor. Various writers have argued that in the colder climates young children move about more freely during the summer months.

The seasonal incidence of poliomyelitis has been a puzzling phenomenon, and one difficult for many to reconcile with the theory that poliomyelitis is spread mainly by droplet infection. As Frost (F 71), however, points out, “diseases which are directly transmissible may and do have very different distributions in nature. For instance, measles, diphtheria, influenza, tuberculosis, and cerebro-spinal meningitis are all, so far as is known, transferred in essentially the same way. Yet their distribution in nature, their rates of prevalence, their apparent contagiousness and many other epidemiological features, are widely different. Hence the premise that poliomyelitis is directly transferred from person to person does not, by itself, justify any definite deduction as to how the disease will be distributed in nature.”

This observation applies to the seasonal distribution with especial force. Droplet infections are not, as is sometimes loosely stated, “cold weather diseases.” Of the most common diseases believed to be so spread, the month of greatest expectancy, and the next greatest are, according to the reports of the United States Public Health Service for 1929 (U 4):

| <i>Disease</i>                | <i>Month of<br/>Highest<br/>Expectancy</i> | <i>Month of Next<br/>Highest<br/>Expectancy</i> |
|-------------------------------|--------------------------------------------|-------------------------------------------------|
| Diphtheria.....               | November                                   | October                                         |
| Measles.....                  | May                                        | April                                           |
| Meningococcus meningitis..... | March                                      | December                                        |
| Scarlet fever.....            | January                                    | March                                           |
| Whooping cough.....           | May                                        | March                                           |



Such a wide distribution of droplet infections throughout the year does not seem to warrant the seasonal distribution as an argument against this mode of spread.

#### PERIODICITY

**Irregularity.** The epidemic prevalence of poliomyelitis is extremely irregular. Some localities have reported a tendency to exacerbations at fairly regular periods, but this has not been the rule. In the populous centers of Northeastern United States, where poliomyelitis has been common, epidemic years are, in general, spaced by 3 to 5 years. Individual localities may, however, escape with only sporadic cases from year to year, while others report recurrences spaced by so short a time as 2-year intervals.

Reference has previously been made (under *Geographic*) to the variations in endemic and epidemic prevalence. Forsbeck and Luther (F57) state that in Massachusetts, poliomyelitis is the most variable of the common communicable diseases in yearly incidence. The highest incidence recorded was in 1916 when 1927 cases were reported, and the lowest number reported in one year (1919) was 66; the former is 29.2 times as large as the latter.

In New Jersey, the range has been even greater. In 1916, 4055 cases were reported, while in the preceding year, 1915, only 36 were recorded. New York State (exclusive of New York City) reported 4215 cases in 1916 and 60 in 1920. In New York City the high (1916) was 9009 cases, the low (1919) 42.

Tables 11 and 17, which show the mean and median cases for the years 1915–1929 for each state, give an idea of the endemic and epidemic conditions which have prevailed in the states. The greater the divergence of the mean from the median, the greater has been the epidemic prevalence.

**Immunity of Affected Localities to Subsequent Epidemics.** The common experience has been that if a community is affected one year with an outbreak of poliomyelitis, it will be relatively free for a varying number of years thereafter.

Wernstedt (W 14a) made a careful study of the localization of the Swedish foci of 1905 and 1911. Within none of the places which were the seats of the five principal centers of 1905 did the disease appear epidemically in 1911. But it was more remarkable that in the neighborhood of almost all of the former centers the scenes of the most intense devastation were found in 1911—that is, in most places the 1905 and 1911 centers were immediately adjacent to each other.

The number of years between epidemics varies within wide limits, but we have met with no examples in the literature where the same locality has been ravaged in successive years. The fact that Massachusetts had in 1909 an epidemic of 923 cases, and in 1910, 845 cases is sometimes quoted as an exception to this. The report of the Massachusetts State Board of Health (M22), however, calls attention to the fact that in 1909, the Berkshire district was most severely affected, and the extreme Eastern part of the state. The Connecticut Valley was practically unaffected. In 1910, a large epidemic center existed in Springfield (which in 1909 had only 1 case), while the Connecticut Valley was generally affected, and the city of Fall River had an epidemic as against only 4 cases in 1909. In both years, minor foci existed in Boston.

Wernstedt (W 14a) also called attention to the fact that the counties in Sweden that suffered least in the 1906–1910 period were the ones most severely ravaged in the 1911–1912 epidemic. The county of Jonköpings, which had the highest number of cases (1065) in 1911, had only 11 cases in 1909, and 6 in 1910.

As would be expected there is a tendency for the length of the inter-epidemic interval to be greater after the larger epidemics. It has been many times observed that the lower the incidence in inter-epidemic years, the higher will be the incidence in epidemic years—"the deeper the trough, the higher the peak."

Lavinder, Freeman and Frost (L 16) report the incidence for the boroughs of New York City for the 1916 epidemic and the three preceding years. In Table 19, they show that the incidence in 1916 tended to vary inversely with the incidence for the boroughs in the preceding three years. Table 20, taken from the *Weekly Bulletin*, 20: 393, 1932, New York City Health Department, shows the annual cases, case rate, and deaths in New York City for the years 1911–1931. It will be seen that the incidence in the years preceding the larger epidemics tends to be low.

Dubois (D 22) gives a chart of cases occurring in Zürich, 1909–1921. The most noticeable feature is the very low point to which the number of cases fell in 1918, followed by a small rise in 1919, and an epidemic in 1920.

The incidence in Massachusetts, which is given in Table 21, also illustrates the relative freedom preceding and following the epidemic years.

It is uncertain to what this immunity from further attack following outbreaks of the disease is due. It has been assumed to be due to an extensive immunizing wave accompanying the recognized cases.



TABLE 19  
POLIOMYELITIS, INCIDENCE BY BOROUGH, NEW YORK CITY, 1913-1915, INCLUSIVE,  
AND 1916, WITH RATES PER 100,000\*

| BOROUGH        | CASES BY YEARS |      |      | TOTAL<br>CASES<br>1913-1915 | AVERAGE<br>RATE<br>1913-1915 | RATE 1916 |
|----------------|----------------|------|------|-----------------------------|------------------------------|-----------|
|                | 1913           | 1914 | 1915 |                             |                              |           |
| Manhattan..... | 160            | 80   | 57   | 297                         | 3.80                         | 125.0     |
| Bronx.....     | 62             | 28   | 10   | 100                         | 6.30                         | 112.1     |
| Brooklyn.....  | 75             | 14   | 21   | 110                         | 2.00                         | 246.0     |
| Queens.....    | 7              | 6    | 7    | 20                          | 1.97                         | 318.3     |
| Richmond.....  | 1              | 1    | 0    | 2                           | 0.71                         | 300.0     |

\* Lavinder, Freeman and Frost, Public Health Bulletin, 91, 1918.

TABLE 20  
POLIOMYELITIS, NEW YORK CITY, 1911-1931; CASES, CASE RATE AND DEATHS\*

| YEAR | CASES | CASE RATE PER 1,000 | DEATHS |
|------|-------|---------------------|--------|
| 1911 | 358   | 0.073               | —      |
| 1912 | 504   | 0.099               | 70     |
| 1913 | 310   | 0.060               | 54     |
| 1914 | 129   | 0.024               | 34     |
| 1915 | 95    | 0.017               | 13     |
| 1916 | 9,023 | 1.610               | 2,448  |
| 1917 | 139   | —                   | 53     |
| 1918 | 134   | —                   | 28     |
| 1919 | 42    | 0.008               | 15     |
| 1920 | 154   | 0.030               | 40     |
| 1921 | 588   | 0.100               | 143    |
| 1922 | 224   | 0.040               | 51     |
| 1923 | 577   | 0.100               | 54     |
| 1924 | 344   | 0.060               | 90     |
| 1925 | 307   | 0.050               | 102    |
| 1926 | 111   | 0.020               | 34     |
| 1927 | 537   | 0.090               | 76     |
| 1928 | 572   | 0.100               | 149    |
| 1929 | 71    | 0.010               | 25     |
| 1930 | 78    | 0.011               | 13     |
| 1931 | 4,138 | 0.583               | 505    |

\* New York City Health Department (Personal Communication).

The neutralization tests reported by Kramer and Aycock (K 24) upon children in the small town of Bedford, Massachusetts, following an outbreak of the disease would seem, however, to indicate that it is not due

to any marked increase in specific immunity. In October, 1930, 5 frank cases of poliomyelitis occurred in Bedford, a town of 1700 inhabitants (an incidence of 294 per 100,000. The incidence in New York City in 1916 was 185 per 100,000). Five months later, the authors tested 20 Bedford children who had passed through minor illnesses at the time of the epidemic (possibly abortive poliomyelitis), and 28 who had remained well. As a comparison they tested 29 children of similar ages from Burlington, Massachusetts, where no poliomyelitis had occurred. The results of the immunity tests in these three groups of children proved to be almost identical, and to correspond with normal children previously tested. (See Table 77.)

TABLE 21  
POLIOMYELITIS CASES, MASSACHUSETTS, 1907-1931\*

| YEAR | CASES | YEAR | CASES |
|------|-------|------|-------|
| 1907 | 234   | 1920 | 696   |
| 1908 | 136   | 1921 | 233   |
| 1909 | 923   | 1922 | 217   |
| 1910 | 845   | 1923 | 223   |
| 1911 | 260   | 1924 | 277   |
| 1912 | 169   | 1925 | 167   |
| 1913 | 361   | 1926 | 245   |
| 1914 | 151   | 1927 | 1,189 |
| 1915 | 135   | 1928 | 434   |
| 1916 | 1,927 | 1929 | 119   |
| 1917 | 174   | 1930 | 503   |
| 1918 | 99    | 1931 | 1,428 |
| 1919 | 66    |      |       |

\* Figures by courtesy of Dr. Gaylord W. Anderson, Massachusetts State Board of Health.

These results are in contrast to those of Dudley in relation to diphtheria (D 27: see original quotation). He showed that in an English school immunity to diphtheria was developed, not continuously but in two steps, each of which was coincident with an outbreak of diphtheria. The development of immunity did not take place in the absence of the disease, but only when it was prevalent clinically.

A small series of neutralization tests, reported by Fairbrother and Brown (F 5), upon children in a boarding school in England following an outbreak of poliomyelitis (see Table 76), agree with those of Dudley. The conditions were much more nearly comparable, *i.e.*, both were in



a “semi-isolated community,” a boarding school, whereas Aycock’s results were on day scholars residing at home.

Neither series can, of course, be considered large enough to more than raise the point.

*Tendency of Poliomyelitis to Revisit Areas Previously Affected.* Lovett and Richardson (L 71a) pointed out, that, while localities which had been the seat of an epidemic tended to remain free for a few years

TABLE 22  
POLIOMYELITIS, 1912-1930, IN 3 CITIES OF NEW YORK STATE\*

| YEAR | BUFFALO |                     |        | ROCHESTER |                     |        | SYRACUSE |                     |        |
|------|---------|---------------------|--------|-----------|---------------------|--------|----------|---------------------|--------|
|      | Cases   | Case rate per 1,000 | Deaths | Cases     | Case rate per 1,000 | Deaths | Cases    | Case rate per 1,000 | Deaths |
| 1912 | —       | —                   | —      | 17        | 0.078               | 3      | —        | 0.014               | —      |
| 1913 | 17      | 0.038               | 3      | 2         | 0.008               | 1      | 14       | 0.096               | 1      |
| 1914 | 9       | 0.020               | 2      | 1         | 0.004               | 0      | 4        | 0.027               | 2      |
| 1915 | —       | —                   | —      | 77        | 0.304               | 3      | 0        | 0                   | 0      |
| 1916 | 13      | 0.028               | 5      | 12        | 0.043               | 2      | 229      | 1.471               | 64     |
| 1917 | —       | —                   | —      | 8         | 0.029               | 0      | 5        | 0.031               | 1      |
| 1918 | 7       | 0.015               | 1      | 9         | 0.032               | 3      | 1        | 0.005               | 1      |
| 1919 | 3       | 0.006               | 0      | 1         | 0.003               | 0      | 0        | 0                   | 0      |
| 1920 | 1       | 0.002               | 0      | 3         | 0.010               | 1      | 1        | 0.005               | 0      |
| 1921 | 14      | 0.030               | 5      | 9         | 0.030               | 1      | 15       | 0.08                | 2      |
| 1922 | 4       | 0.010               | 2      | 4         | 0.012               | 4      | 50       | 0.25                | 11     |
| 1923 | 11      | 0.020               | 2      | 2         | 0.006               | 2      | 8        | 0.04                | 1      |
| 1924 | 34      | 0.060               | 4      | 5         | 0.020               | 0      | 152      | 0.71                | 12     |
| 1925 | 40      | 0.070               | 11     | 28        | 0.090               | 8      | 5        | 0.03                | 2      |
| 1926 | 144     | 0.260               | 15     | 9         | 0.030               | 1      | 66       | 0.35                | 13     |
| 1927 | 14      | 0.030               | 1      | 7         | 0.020               | 3      | 2        | 0.01                | 0      |
| 1928 | 27      | 0.050               | 12     | 15        | 0.050               | 4      | 25       | 0.13                | 2      |
| 1929 | 102     | 0.180               | 16     | 32        | 0.100               | 10     | 24       | 0.12                | 5      |
| 1930 | 75      | 0.131               | 8      | 68        | 0.210               | 15     | 150      | 0.74                | 15     |

\* This table has been compiled from the United States Public Health Reports, The Notifiable Diseases, Prevalence in Large Cities, 1912-1930.

thereafter, they were more liable to be revisited than places less heavily affected, where the disease seems to continue year after year with about the same number of cases. The examples most frequently cited to illustrate this tendency are the New York cities of Buffalo, Rochester and Syracuse. In Table 22 is given the number of cases, the case rate, and the deaths for these three cities for the years since the disease was made reportable.

The explanation which has usually been given to this tendency of the disease to revisit areas is that reservoirs of infection, possibly carriers, remain. It is possible, however, especially in view of the above results of Kramer and Aycock, that the tendency to return to a locality is due to something in that particular environment which lowers the non-specific resistance.

**Explanations Offered for Periodicity of the Disease.** A great deal of thought has been expended in an effort to explain why poliomyelitis, which is constantly present in endemic form, should at certain intervals and in certain places assume epidemic proportions. The question, while exceedingly interesting, is not peculiar to poliomyelitis, for it has not been satisfactorily answered in regard to other diseases. The explanations most frequently met are:

*Accumulation of Susceptible Persons.* The problem of periodicity is rendered even more complex in poliomyelitis than in some other diseases by the fact, which we emphasize later that susceptibility to poliomyelitis lies not only in a lack of specific immunity, but also in a lack of nonspecific resistance. The accumulation of these two types of susceptible persons may depend upon entirely different factors. The fact that the age incidence does not vary materially from year to year even in epidemics which occur after a number of years of comparative freedom from the disease has been taken by Aycock (A 34) to mean that the accumulation of non-immunes is not a major factor in the production of epidemics. This argument would also apply to the possible accumulation of those lacking nonspecific resistance.

*Meteorological Conditions.* Numerous attempts have been made to show a correlation between various meteorological conditions and outbreaks of poliomyelitis, but without success. Epidemic years may be years of excessive rainfall, or the reverse. There are many examples of both. Nor has it been shown that epidemic years are marked by greater or less humidity than normal though there is the possibility that atmospheric humidity may bear a purely mechanical relation to the facility with which infective droplets are exchanged.

With temperature, however, and the incidence of poliomyelitis there appears to be a positive correlation. Outbreaks as well as endemic incidence ordinarily follow in the main the curves for temperature. The fall in the severity of epidemics is more apt to be synchronized with the decline in temperature than is the rise in incidence to be related to rising temperature. We have not, however, noted that outbreaks are more apt to occur in years that vary from the normal, either as to an excessive



or a deficient temperature. The relation to temperature is not, moreover, a necessary one, for cases, and even epidemics, have occurred at all seasons of the year.

Reference has been made under *Geographic Distribution* to the fact that poliomyelitis is more prevalent where there is a marked seasonal fluctuation in temperature.

#### INCUBATION PERIOD

The estimates of the incubation period of poliomyelitis are for the most part based upon familial outbreaks and cases where exposure to other cases is known to have occurred. In the *Section on Carriers*, attention is called to the fact that if the disease is transmitted only from person to person, healthy carriers are probably numerous. Failure to recognize that multiple cases might be common source infections, a lack of understanding of the extensive rôle which carriers may play in the transmission of the disease, led to the estimation by the earlier workers of an incubation period now believed to be too short. The most valuable evidence for fixing the incubation period of a disease is derived from an accumulation of cases exposed to a source of infection for one day only. Obviously the higher the estimated carrier rate in a disease, the less sure can one be that the recognized exposure is the only one. Even in the relatively infrequent instances in which cases give a history of contact with another case, there is the possibility that both may have been exposed to the same or a different carrier.

Wickman (W 21) estimated from the interval which elapsed between the first and second cases in families that the period of incubation was 1 to 4 days and is usually quoted to this effect. Later, however, he found that in some cases, in which the disease apparently developed after a visit that the incubation period was 6 to 10 days. In 6 cases in which the source of infection and the duration of exposure were definitely known, the minimum incubation was 5 days, the average about 7. He concluded that his earlier estimate had been based upon common source infections and that 6 to 10 days was more likely the true incubation period.

Emerson (N 20) made, during the 1916 epidemic in New York, a distinction between the apparent and determined incubation periods; 584 cases fell into the first and 15 into the second category. One-third of the latter fell on the third day, and two-thirds within eight days. He concluded, however, that "a larger number of 'determined' incubation periods must be assembled before we shall know whether the figures obtained represented the true period."

Lavinder, Freeman and Frost (L 16) made in 1916 a study of the cases who had left New York City and subsequently developed the disease. Considering only those who were the first case in the community where they developed, and who were therefore presumably infected prior to leaving New York City, we may conclude from Table 23 that the incubation period was not under 7 days—though the number of days over 7 cannot be determined, since it is impossible to estimate how long before leaving New York the cases were infected.

TABLE 23

DEVELOPMENT OF CASES OF POLIOMYELITIS IN PERSONS FROM NEW YORK CITY,  
WHO DEVELOPED THE DISEASE IN COMMUNITIES APPARENTLY  
FREE FROM INFECTION\*

| INTERVAL BETWEEN DEPARTURE FROM NEW YORK CITY AND ONSET | CASES |
|---------------------------------------------------------|-------|
| Same day.....                                           | 2     |
| 1 day.....                                              | 4     |
| 2 days.....                                             | 2     |
| 3 days.....                                             | 4     |
| 4 days.....                                             | 0     |
| 5 days.....                                             | 2     |
| 6 days.....                                             | 4     |
| 7 days.....                                             | 5     |
| 8 days.....                                             | 0     |
| 9 days.....                                             | 1     |
| 10 days.....                                            | 0     |
| 11 days.....                                            | 0     |
| 12 days.....                                            | 1     |
| Over 12 days.....                                       | 3     |

\* Lavinder, Freeman and Frost, Public Health Bulletin, 91, 1918.

Wernstedt (W 14) believes it an error to estimate the interval between cases occurring in the same family. On the basis of 45 of his cases, in whom he felt that he could determine the interval with some degree of accuracy, he concluded that the incubation period was seldom less than 4 and seldom more than 12 days, being usually 4 to 7 days.

Müller (M 55) estimated the incubation period at 6 to 9 days; Dubois (D 22), 2 to 8 days; MacNalty (M 10), 2 to 10 days, with an average of 3 to 4 days; The White House Conference, Section on Communicable Diseases (W 18), 7 to 14 days.

Aycock and Luther (A 49) have attempted to correlate the evidence as to the incubation period from a number of sources. Since polio-



myelitis is subject to considerable variation in the manner of its onset, they have considered the appearance of febrile symptoms with meningeal signs as the onset in all types of the disease.

They have estimated the duration of the incubation period from evidence obtained by study of (1) milk-borne outbreaks, (2) cases following tonsillectomy, (3) contact cases with limited exposure, and (4) experimental disease.

(1) **Milk-borne Outbreaks** (for details of these outbreaks, see under *Transmission by Milk*).

Wickman (W 21) reported an outbreak in which the primary case, with onset on October 6 was followed on October 20 by 5 other cases.

Dingman (D 13) reported an interval between the primary and secondary cases between 14 and 18 days. But from the time that certain of the cases began or discontinued the use of milk, the incubation periods were probably not under 6, and not over 14 days.

Knapp, Godfrey, and Aycock (K 17) reported that in Cortland, New York, the interval between the primary case and 6 of the secondary cases was from 7 to 12 days, while in 2 cases, the interval was 18 days.

Aycock (A 33) reports that in Broadstairs, England, 4 individuals either arrived or left shortly before the outbreak. These fixed within a period of 3 days the time during which the milk supply was probably contaminated, the majority of cases occurring from 7 to 14 days following this period.

*Summary.* In the above outbreaks, the apparent incubation period of the disease varied from 6 to 18 days.

(2) **Cases Following Tonsillectomy.** Aycock and Luther (A 50) reported that of 36 cases giving a history of tonsillectomy within a year, 16 had had the operation within one month preceding the development of the disease. Of these 16, all developed between 7 and 18 days following the operation, *i.e.*, no cases developed under 7 days, and none from the eighteenth to the thirtieth day.

The frequency of this interval between tonsillectomy and the onset of the disease suggests a causal relationship, with an incubation period from 7 to 18 days.

(3) **Contact Cases with a Limited Exposure.** The authors analyzed a number of cases, some in the same family, others not, in which the time of exposure could be fixed within a limited period. In all cases where the duration of exposure was so brief as a single day, the incubation period must have fallen between 6 and 20 days, except in one instance, where there were two single exposures—3 and 10 days preceding the on-

set of the second case. They regard the earlier exposure as the significant one. It also appeared that in all cases where the interval between the last exposure and the onset was less than 6 days, the duration of exposure was such that the incubation period could have been more than 6 days.

(4) **Incubation Period of Experimental Poliomyelitis.** The incubation period of monkeys following single intracerebral inoculations with unmodified virus varied in the authors' experience, from 4 to 15 days, with most coming down on the fifth to eighth day. Virus, modified by the action of immune serum, disinfectants, or other means showed a longer interval.

Various workers have given incubation periods in the experimental disease as:

| <i>Author</i>                       | <i>Reference</i> | <i>Incubation Period<br/>in Days</i> |
|-------------------------------------|------------------|--------------------------------------|
| Leiner and von Wiesner.....         | L 28, I          | 6-10                                 |
| Flexner and Lewis.....              | F 47             | 9.82                                 |
| Leake.....                          | L 18             | 4-11                                 |
| Levaditi.....                       | L 34             | 5-8                                  |
| Zappert.....                        | Z 2              | 9.5                                  |
| Harmon, Shaughnessy and Gordon..... | H 14             | 7-11                                 |
| Brodie.....                         | B 31             | 7.9                                  |
| Aycock and Luther.....              | A 50             | 4-15, usually 5-8                    |

From the evidence obtained from these various sources, Aycock and Luther conclude: In all cases where the time of exposure can be set within narrow limits, the apparent incubation falls within a period of from 6 to 20 days. In all cases where the last exposure occurred less than 6 days preceding the onset of the secondary case, the duration of exposure is such that the incubation period could likewise have fallen within these limits; in no case, therefore, was the incubation period necessarily shorter than 6 days.

#### CASE FATALITY

**Inverse Relationship between Case Incidence and Case Fatality.** The case fatality of poliomyelitis varies within very wide limits. While one might expect that in years of epidemic prevalence, the case fatality would be high, no such correspondence is noted. In general, the case fatality is inversely proportional to the number of cases. This is true of other diseases also, but the relation is more marked in the case of poliomyelitis. It is observed more consistently that the case fatality is high in years of low prevalence, than that the case fatality is low in years of high prevalence, though this also is the usual experience.



CHART VII

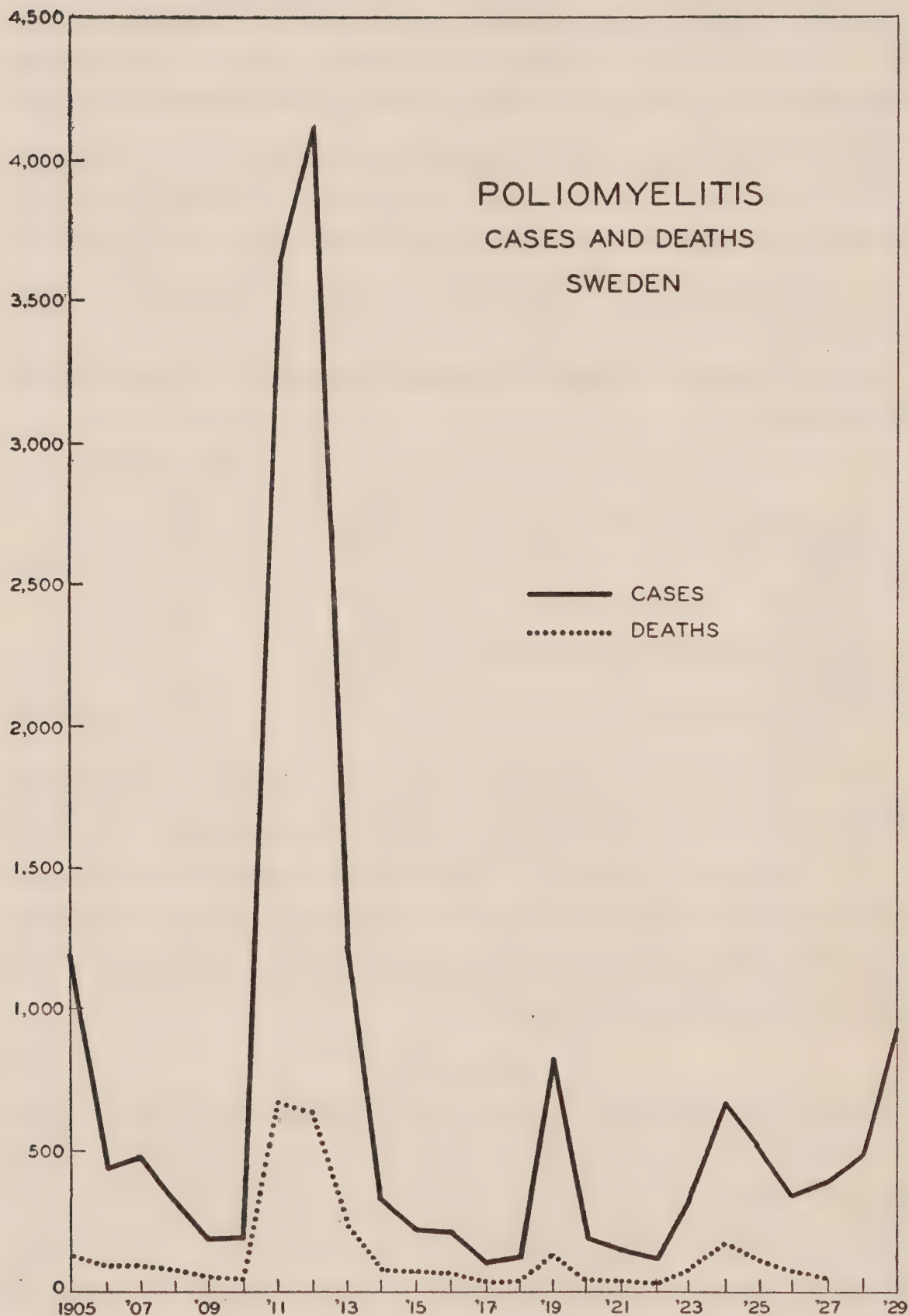


CHART VII. Poliomyelitis, Sweden. Cases, 1905-1929, and deaths, 1905-1927. The case fatality is seen to be low in the epidemic years, and high in the inter-epidemic years. (Figures from the League of Nations, Monthly Epidemiological Report, February 15, 1930.)

Since to assume a low virulence of the virus when the disease assumes epidemic proportions is not reasonable, this has been attributed to dif-

TABLE 24  
POLIOMYELITIS IN SWEDEN, 1903-1929\*

| YEAR       | CASES  | CASE RATE<br>PER 100,000 | DEATHS | DEATH RATE<br>PER 100,000 | CASE FATALITY |
|------------|--------|--------------------------|--------|---------------------------|---------------|
| 1903       | —      | —                        | 2†     | 0.4                       | —             |
| 1904       | —      | —                        | 1†     | 0.2                       | —             |
| 1905       | 1,199  | 22.7                     | 134    | 2.5                       | 11.2          |
| 1906       | 429    | 8.1                      | 90     | 1.7                       | 21.0          |
| 1907       | 467    | 8.7                      | 96     | 1.8                       | 20.6          |
| 1908       | 316    | 5.8                      | 80     | 1.5                       | 25.3          |
| 1909       | 172    | 3.2                      | 50     | 0.9                       | 29.1          |
| 1910       | 186    | 3.4                      | 49     | 0.9                       | 26.3          |
| 1911       | 3,646  | 66.3                     | 662    | 11.9                      | 18.2          |
| 1912       | 4,112  | 73.7                     | 632    | 11.3                      | 15.4          |
| 1913       | 1,220  | 21.7                     | 231    | 4.1                       | 18.9          |
| 1914       | 325    | 5.7                      | 73     | 1.3                       | 22.5          |
| 1915       | 214    | 3.8                      | 64     | 1.1                       | 30.0          |
| 1916       | 207    | 3.6                      | 59     | 1.0                       | 28.5          |
| 1917       | 99     | 1.7                      | 31     | 0.5                       | 31.3          |
| 1918       | 122    | 2.1                      | 37     | 0.6                       | 30.3          |
| 1919       | 820    | 14.1                     | 132    | 2.3                       | 16.0          |
| 1920       | 181    | 3.1                      | 42     | 0.7                       | 23.2          |
| 1921       | 141    | 2.4                      | 40     | 0.7                       | 28.4          |
| 1922       | 112    | 1.9                      | 29     | 0.5                       | 25.9          |
| 1923       | 309    | 5.2                      | 73     | 1.2                       | 23.6          |
| 1924       | 656    | 10.9                     | 166    | 2.8                       | 25.3          |
| 1925       | 517    | 8.6                      | 101    | 1.7                       | 19.5          |
| 1926       | 341    | 5.6                      | 67     | 1.1                       | 19.6          |
| 1927       | 385    | 6.3                      | 49     | 0.8                       | 13.1          |
| 1928       | 485†   | 8.0                      | —      | —                         | —             |
| 1929       | 937†   | 15.4                     | —      | —                         | —             |
| Total..... | 16,176 | —                        | 2,887  | —                         | 17.9          |

\* League of Nations, Monthly Epidemiological Report, February 15, 1930, p. 52.

† If both cases and deaths are not available for a given year, they are omitted from the total.

ferences in reporting nonparalytic and abortive cases in epidemic and inter-epidemic years. During an epidemic, the attention of both physicians and the public is directed to the disease, which results in



more complete recognition of the mild forms of the disease, and quite possibly to the reporting of other conditions as poliomyelitis. In years of few cases, the milder forms are less often diagnosed, and the case fatality represents more nearly the ratio of deaths to paralytic cases.

TABLE 25  
POLIOMYELITIS IN KANSAS, 1908-1930\*

The case fatality is seen to be highest in years of low prevalence, lowest in years of high prevalence.

| YEAR       | CASES | DEATHS | CASE FATALITY |
|------------|-------|--------|---------------|
| 1908       | 100   | 33     | 33.0          |
| 1909       | 90    | 27     | 30.0          |
| 1910       | 196   | 53     | 27.0          |
| 1911       | 26    | 8      | 30.7          |
| 1912       | 70    | 23     | 32.8          |
| 1913       | 16    | 6      | 37.5          |
| 1914       | 26    | 13     | 50.0          |
| 1915       | 29    | 17     | 58.6          |
| 1916       | 120   | 26     | 21.6          |
| 1917       | 75    | 17     | 22.6          |
| 1918       | 30    | 12     | 40.0          |
| 1919       | 60    | 17     | 28.3          |
| 1920       | 26    | 8      | 30.7          |
| 1921       | 91    | 33     | 36.2          |
| 1922       | 23    | 20     | 86.9          |
| 1923       | 149   | 36     | 24.1          |
| 1924       | 28    | 12     | 42.8          |
| 1925       | 122   | 36     | 29.5          |
| 1926       | 66    | 20     | 30.3          |
| 1927       | 196   | 49     | 25.0          |
| 1928       | 40    | 9      | 22.5          |
| 1929       | 26    | 10     | 38.4          |
| 1930       | 694   | 64     | 9.1           |
| Total..... | 2,299 | 549    | 23.8          |

\* Brown, J. Kansas M. S. 33: 81, 1932.

The errors which may be referable to reporting are, in the case of poliomyelitis, so large that other factors influencing the case fatality tend to be obscured. This is to be considered both in comparing epidemic and non-epidemic years, and in comparing epidemics of different years. During the 1916 epidemic, for example, very few cases were

reported unless they developed paralysis. Since in 1931 only 43 per cent of reported cases were paralytic, an allowance must be made for these in comparing fatalities. Under *Prognosis*, it has been shown that if the ratio between nonparalytic and paralytic cases was the same in 1916 and 1931, the case fatality was also approximately the same.

The figures for Sweden as reported by the League of Nations (L 17) illustrate the tendency for the number of cases and the case fatality to be inversely proportional. The case fatality was highest in 1917, the year of fewest cases since 1905. The years of high incidence have invariably shown a low case fatality. These figures are given in Table 24.

Table 25, showing the incidence of poliomyelitis in Kansas, 1908-1930, is taken from the report by Brown (B 34). The inverse relationship which exists between the number of cases and the case fatality is here

TABLE 26  
MORBIDITY, MORTALITY, AND CASE FATALITY IN SAXONY, 1927\*

| AGE                    | MORBIDITY<br>PER 10,000<br>POPULATION | MORTALITY<br>PER 100,000<br>POPULATION | CASE FATALITY |
|------------------------|---------------------------------------|----------------------------------------|---------------|
| Under 6 years.....     | 6.9                                   | 6.33                                   | 9.14          |
| 6 to 14 years.....     | 2.6                                   | 3.47                                   | 12.92         |
| 14 years and over..... | 0.12                                  | 0.38                                   | 30.0          |

\* Krahn, Arch. f. Hyg. 101: 65, 1929.

so marked that any explanation other than errors in reporting would be impossible.

The case fatality in New York City and New York State has not shown this relation so regularly. From Table 32, given under *Case Fatality among Urban and Rural Cases* it is seen that 1916, the highest recorded, showed a high case fatality, although 1931, the next highest year, showed a very low case fatality. The years between have also not shown so definite a relationship between the number of cases and the fatality as most other localities.

**Case Fatality, Dependent upon Type of Disease.** Under *Prognosis, Chapter on Symptomatology*, there is discussed the relation which the clinical type of disease bears to the case fatality.

**Influence of Age upon Case Fatality.** Age exerts a marked effect upon the outcome of cases of poliomyelitis. In general, the case fatality is highest in infants under a year and in the older age groups, where the incidence is low, and lowest in the ages where the incidence is high.



Why persons in the ages which are best able to resist infection should, once infected, succumb more frequently, has not been satisfactorily explained.

Thus Krahn (K 23) reports that in the Saxony epidemic in 1927, 70 of 587 cases died, a case fatality of 12 per cent. Table 26 gives the morbidity per 10,000 and mortality per 100,000 population, and the case fatality for this epidemic.

TABLE 27  
CASE FATALITY BY STANDARD AGE PERIODS, NEW YORK CITY, 1916 AND 1931

| AGE PERIODS            | 1916* |        |          | 1931† |        |          |
|------------------------|-------|--------|----------|-------|--------|----------|
|                        | Cases | Deaths | Fatality | Cases | Deaths | Fatality |
| Under 1 year.....      | 1,014 | 358    | 35.3     | 165   | 32     | 19.3     |
| Under 5 years.....     | 7,231 | 1,713  | 23.7     | 2,090 | 233    | 11.1     |
| 5 to 9 years.....      | 1,483 | 379    | 25.6     | 1,205 | 146    | 12.1     |
| 10 to 14 years.....    | 225   | 63     | 25.6     | 402   | 57     | 14.1     |
| 15 to 19 years.....    | 78    | 24     | 32.5     | 114   | 35     | 30.7     |
| 20 to 24.....          | 31    | 13     | 41.9     | 50    | 17     | 34.0     |
| 25 to 34 years.....    | 59    | 19     | 32.2     | 43    | 11     | 25.5     |
| 35 years and over..... | 24    | 7      | 29.1     | 14    | 5      | 35.7     |
| Unknown.....           | 214   | 25     | —        | 182   | —      | —        |
| Totals.....            | 9,345 | 2,243  | 24.0     | 4,100 | 504    | 12.3     |

\* Lavinder, Freeman and Frost, Public Health Bulletin, 91, 1918.  
† Courtesy of the New York City Health Department.

The case fatality in the epidemic in Alsace in 1930 showed a similar relation to age. Levaditi, Schmutz and Willemin (L 51) report that 39 of 405 cases died, a case fatality of 9.6 per cent. As to age:

|                    | <i>Per Cent</i> |
|--------------------|-----------------|
| Preschool age..... | 7.5             |
| School age.....    | 16.0            |
| Adolescents.....   | 20.0            |

In Table 27 we have compared the case fatality during the 1916 and the 1931 epidemics in New York City. We have elsewhere explained that the fact that in 1931, 43 per cent of the cases were nonparalytic, while in 1916, relatively few such cases were reported, accounts in large measure for the difference in case fatality. In Table 27, therefore, we do not wish to contrast the case fatality in the two epidemics, but to show that a similar relation to age maintained.

CHART VIII  
POLIOMYELITIS  
CASE FATALITY BY AGE GROUPS  
IN FOUR EPIDEMICS

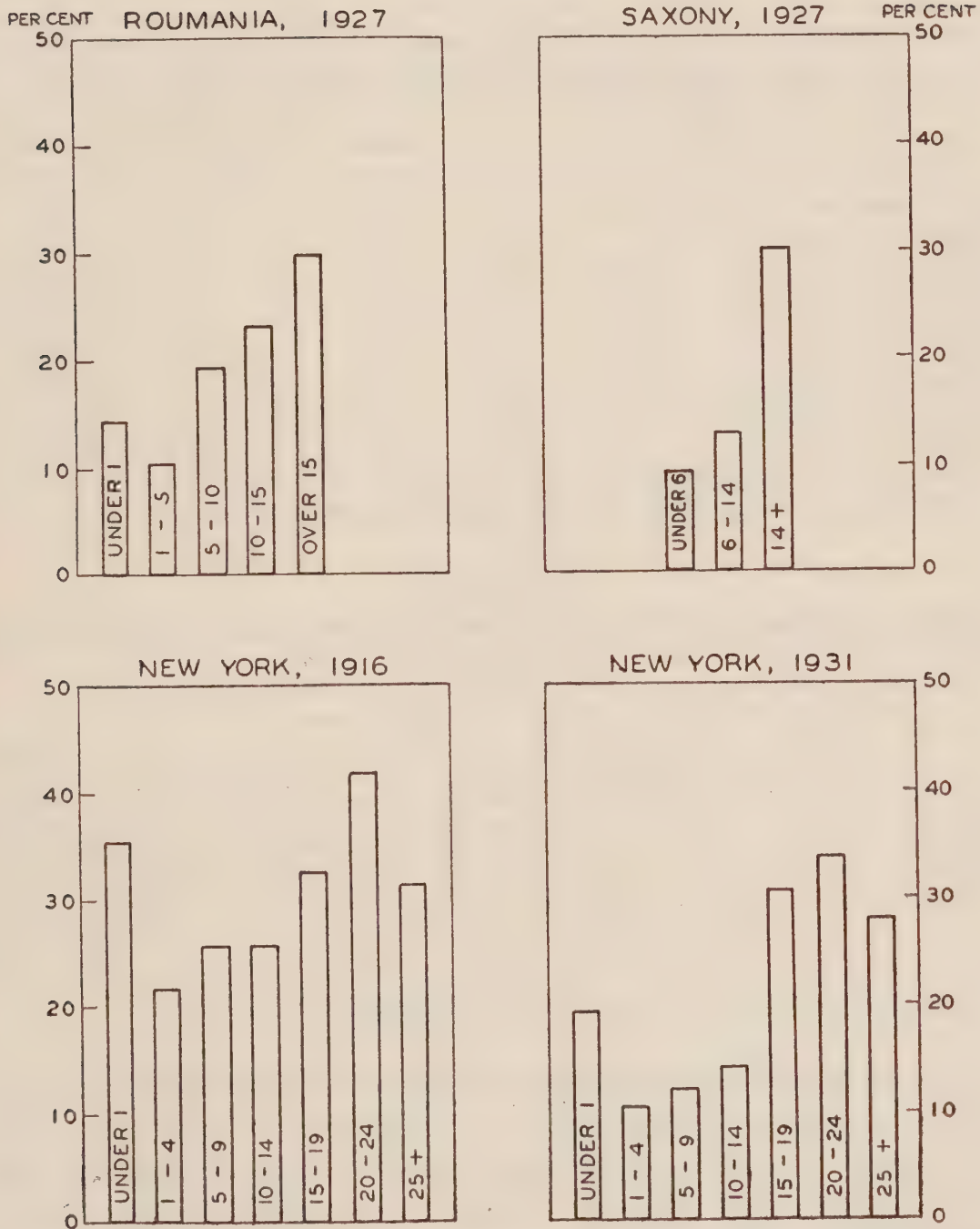


CHART VIII. Poliomyelitis. Case fatality by age, in four epidemics: Roumania, 1927 (League of Nations, Monthly Epidemiological Reports, February 15, 1930); Saxony, 1927 (Krahn, Arch. f. Hyg., 101: 65, 1927); New York City, 1916 (Public Health Bulletin, 91, 1918); New York City, 1931 (figures by courtesy of New York City Health Department).



*Case Fatality in Infants under One Year.* Weisenburg (W 12) gives comparable figures for cases at the Municipal Hospital, Philadelphia in 1916. His figures also show the high fatality under one year, and in older persons. Among the 49 cases which were breast-fed, there were only 7 deaths. We have been unable to locate other data on the influence of maternal nursing on case fatality.

TABLE 28  
CASES AND DEATHS BY AGE GROUPS, MUNICIPAL HOSPITAL, PHILADELPHIA, 1916\*

| AGE GROUP               | CASES | DEATHS | CASE FATALITY |
|-------------------------|-------|--------|---------------|
| Under 6 months.....     | 37    | 17     | 45.9          |
| 6 months to 1 year..... | 138   | 57     | 41.3          |
| 1 to 4 years.....       | 442   | 62     | 14.0          |
| 5 to 9 years.....       | 64    | 14     | 21.8          |
| 10 to 19 years.....     | 18    | 8      | 44.4          |
| 20 years and over.....  | 8     | 2      | 25.0          |
| Total.....              | 707   | 160    | 22.6          |

\* Weisenburg, Trans. Am. Neur. Assn. 43: 142, 1918.

TABLE 29  
POLIOMYELITIS, CASES AND DEATHS IN PATIENTS UNDER 1 YEAR, NEW YORK CITY, JUNE 1 TO NOVEMBER 1, 1916\*

|             | AGE IN MONTHS |    |    |      |    |    |      |     |     |      |     |     | TOTAL |
|-------------|---------------|----|----|------|----|----|------|-----|-----|------|-----|-----|-------|
|             | Under 1       | 1  | 2  | 3    | 4  | 5  | 6    | 7   | 8   | 9    | 10  | 11  |       |
| Cases.....  | 7             | 19 | 27 | 52   | 70 | 64 | 98   | 118 | 104 | 153  | 149 | 121 | 982   |
| Deaths..... | 3             | 13 | 10 | 17   | 24 | 34 | 45   | 45  | 44  | 52   | 73  | 63  | 423   |
|             | 49.0          |    |    | 40.3 |    |    | 41.8 |     |     | 44.4 |     |     | 43.0  |

\* New York City Health Department Monograph, 1916, p. 376.

The New York City Department of Health (N 20) reported the distribution of cases and deaths under 1 year in New York City in 1916, and the case fatality in three month periods. This is given in Table 29. The total case fatality for all ages for the epidemic was, as shown in Table 27, 24 per cent.

Godfrey (G 10) gives the percentage of total cases and deaths, and fatality rate at each age in New York State, at all places under 200,000 population, 1920-1924.

The League of Nations, Monthly Epidemiological Report for February 15, 1930 (L 17) gives the age incidence in Roumania in 1927 which shows a similar case fatality by age groups.

*Case Fatality of Poliomyelitis, as Compared with Other Diseases as to Age.* Lavinder, Freeman and Frost (L 16) also compare the case

TABLE 30  
CASES, DEATHS AND FATALITY RATE BY AGE GROUPS IN NEW YORK STATE AT ALL PLACES UNDER 200,000 POPULATION, 1920-1924\*

| AGE                    | PER CENT OF ALL AGES |        | FATALITY RATE   |
|------------------------|----------------------|--------|-----------------|
|                        | Cases                | Deaths |                 |
|                        |                      |        | <i>per cent</i> |
| Under 1 year.....      | 4.3                  | 6.8    | 26.1            |
| Under 5 years.....     | 42.5                 | 36.6   | 14.0            |
| 5 to 9 years.....      | 24.2                 | 19.6   | 13.2            |
| 10 to 14 years.....    | 15.0                 | 17.3   | 18.9            |
| 15 to 19 years.....    | 8.7                  | 7.7    | 14.4            |
| 20 years and over..... | 9.6                  | 18.8   | 31.7            |

\* Godfrey, Am. J. Pub. Health, 18: 616, 1928.

TABLE 31  
CASES, DEATHS AND CASE FATALITY BY AGE GROUPS, ROUMANIA, 1927\*

| AGE                 | CASES  |                   | DEATHS |                   | CASE FATALITY |
|---------------------|--------|-------------------|--------|-------------------|---------------|
|                     | Number | Per cent of total | Number | Per cent of total |               |
| 0 to 1 year.....    | 442    | 16.9              | 46     | 15.8              | 14.07         |
| 1 to 5 years.....   | 1,960  | 75.2              | 201    | 69.0              | 10.2          |
| 5 to 10 years.....  | 126    | 4.8               | 24     | 8.2               | 19.0          |
| 10 to 15 years..... | 39     | 1.5               | 9      | 3.1               | 23.0          |
| Over 15 years.....  | 37     | 1.4               | 11     | 3.7               | 29.7          |
| Total.....          | 2,604  | —                 | 291    | —                 | 11.1          |

\* League of Nations, Monthly Epidemiological Report, February 15, 1930.

fatality of poliomyelitis with that for measles, scarlet fever, and diphtheria in New York City in 1916. The three latter diseases are “strikingly similar in their general outlines, the fatality rate being higher in the ages under 5, tending strongly downward during the years of adolescence, and upward again with adult and middle life. Poliomyelitis departs markedly from the other diseases in the general shape of its curve



showing the lowest rate for the group under 5 and tending strongly upward for all higher age groups.”

**Fatality among Rural and Urban Cases.** It has been stated in a number of epidemics that the case fatality has been higher in the urban

TABLE 32  
POLIOMYELITIS, CASES, DEATHS AND RATES, NEW YORK, 1912-1931\*

| YEAR  | STATE (EXCLUSIVE OF NEW YORK CITY) |        |        |       |           | NEW YORK CITY |        |        |       |           |
|-------|------------------------------------|--------|--------|-------|-----------|---------------|--------|--------|-------|-----------|
|       | Cases                              | Deaths | Rates† |       |           | Cases         | Deaths | Rates† |       |           |
|       |                                    |        | Case   | Death | Fatal-ity |               |        | Case   | Death | Fatal-ity |
| 1912  | 629                                | 113    | 14.0   | 2.5   | 18.0      | 501           | 70     | 10.1   | 1.4   | 14.0      |
| 1913  | 181                                | 68     | 4.0    | 1.5   | 37.6      | 310           | 55     | 6.1    | 1.1   | 17.7      |
| 1914  | 95                                 | 34     | 2.1    | 0.7   | 35.8      | 129           | 34     | 2.5    | 0.7   | 26.4      |
| 1915  | 164                                | 34     | 3.5    | 0.7   | 20.7      | 95            | 13     | 1.8    | 0.2   | 13.7      |
| 1916  | 4,215                              | 901    | 89.6   | 19.2  | 21.4      | 9,009         | 2,448  | 169.5  | 46.1  | 27.2      |
| 1917  | 156                                | 39     | 3.3    | 0.8   | 25.0      | 139           | 53     | 2.6    | 1.0   | 38.1      |
| 1918  | 99                                 | 29     | 2.1    | 0.6   | 29.3      | 134           | 28     | 2.4    | 0.5   | 20.9      |
| 1919  | 104                                | 20     | 2.2    | 0.4   | 19.2      | 42            | 15     | 0.8    | 0.3   | 35.7      |
| 1920  | 60                                 | 10     | 1.2    | 0.2   | 16.7      | 154           | 40     | 2.7    | 0.7   | 26.0      |
| 1921  | 565                                | 123    | 11.5   | 2.5   | 21.8      | 588           | 143    | 10.1   | 2.5   | 24.3      |
| 1922  | 393                                | 98     | 7.9    | 2.0   | 24.9      | 224           | 51     | 3.7    | 0.8   | 22.8      |
| 1923  | 367                                | 53     | 7.2    | 1.0   | 14.4      | 577           | 54     | 9.5    | 0.9   | 9.4       |
| 1924  | 870                                | 91     | 16.7   | 1.8   | 10.5      | 344           | 90     | 5.6    | 1.5   | 26.2      |
| 1925  | 488                                | 106    | 9.2    | 2.0   | 21.7      | 307           | 102    | 4.9    | 1.6   | 33.2      |
| 1926  | 564                                | 106    | 10.5   | 2.0   | 18.8      | 110           | 34     | 1.7    | 0.5   | 30.9      |
| 1927  | 378                                | 50     | 6.9    | 0.9   | 13.2      | 537           | 76     | 8.2    | 1.2   | 14.2      |
| 1928  | 447                                | 87     | 8.1    | 1.6   | 19.5      | 572           | 149    | 8.5    | 2.2   | 26.0      |
| 1929  | 424                                | 78     | 7.6    | 1.4   | 18.4      | 71            | 25     | 1.0    | 0.4   | 35.2      |
| 1930  | 660                                | 111    | 11.6   | 2.0   | 16.8      | 78            | 14     | 1.1    | 0.2   | 17.9      |
| 1931‡ | 2,046                              | 156§   | 35.5   | 2.8§  | 7.8§      | 4,138         | 497§   | 58.4   | 7.2§  | 12.1§     |
| Total | 12,905                             | 2,307  | 12.7   | 2.3   | 17.9      | 18,059        | 3,991  | 15.6   | 3.5   | 22.1      |

\* New York State Health Commission, Public Health in New York State, Report State of New York Department of Health, 1932.

† Case and death rates per 100,000 population; fatality, deaths per 100 cases.

‡ Provisional figures.

§ To December 1, 1931. [Later reports from New York City Department of Health gives 505 deaths in New York City, a case fatality of 12.2 for the year.]

than in the rural cases. Frost (F 71) reported that the case fatality within the city of Cincinnati, Ohio, was higher (38.9 per cent) than in the smaller neighboring town of Covington (18.2 per cent), or in the suburban cases (9 per cent).

Godfrey (G 10) pointed out the comparatively high case and death rates in New York City as compared with the rest of the state in the period 1915-1924. This was largely due to the figures for 1916. The case fatality fell somewhat irregularly until the group of villages under 2500 population was reached, when it unaccountably rose.

Table 32, showing the relation between the cases, deaths and rates in New York City and the rest of New York State for the years 1912-1931, has been taken from the report of the New York State Health Com-

TABLE 33  
ANTERIOR POLIOMYELITIS, FATALITY RATES IN MASSACHUSETTS, 1916-1929, BY CERTAIN POPULATION GROUPS\*

| YEAR   | STATE | OVER<br>500,000<br>(BOSTON) | 100,000-<br>500,000 | 50,000-<br>100,000 | 25,000-<br>50,000 | 10,000-<br>25,000 | 5,000-<br>10,000 | 2,500-<br>5,000 | UNDER<br>2,500 |
|--------|-------|-----------------------------|---------------------|--------------------|-------------------|-------------------|------------------|-----------------|----------------|
| 1916   | 23.5  | 32.8                        | 16.3                | 28.0               | 18.4              | 21.1              | 18.5             | 16.0            | 23.1           |
| 1917   | 29.3  | 38.4                        | 45.4                | 13.6               | 22.6              | 41.1              | 25.0             | 25.0            | 25.0           |
| 1918   | 37.4  | 64.3                        | 25.8                | 33.3               | 30.8              | 33.3              | 25.0             | 42.8            | 50.0†          |
| 1919   | 22.7  | 23.0                        | 35.7                | 11.1               | 0                 | 36.4              | 22.2             | 0               | 0              |
| 1920   | 20.7  | 24.6                        | 26.8                | 21.7               | 14.3              | 15.6              | 27.0             | 22.2            | 20.7           |
| 1921   | 20.6  | 27.6                        | 4.2                 | 14.3               | 15.4              | 25.5              | 30.0             | 25.0            | 25.0           |
| 1922   | 15.2  | 23.4                        | 20.0                | 10.7               | 27.8              | 2.4               | 16.7             | 0               | 8.3            |
| 1923   | 15.5  | 22.5                        | 15.7                | 7.4                | 26.1              | 3.1               | 0                | 100.0           | 27.3           |
| 1924   | 9.7   | 10.7                        | 4.9                 | 0                  | 18.7              | 10.0              | 12.1             | 6.7             | 28.6†          |
| 1925   | 31.1  | 28.2                        | 20.8                | 5.6                | 48.2              | 22.2              | 5.4              | 50.0            | 83.3†          |
| 1926   | 18.0  | 53.8                        | 16.0                | 13.0               | 10.0              | 25.5              | 8.3              | 22.2            | 0              |
| 1927   | 14.2  | 23.1                        | 16.7                | 9.6                | 9.8               | 7.7               | 12.1             | 13.2            | 11.1           |
| 1928   | 15.0  | 25.9                        | 15.6                | 28.6               | 8.9               | 7.1               | 2.6              | 15.8            | 36.4           |
| 1929   | 17.6  | 28.1                        | 12.5                | 13.3               | 20.0              | 11.1              | 33.3             | 0               | 16.7           |
| Mean.. | 19.7  | 27.8                        | 17.3                | 19.3               | 15.8              | 16.4              | 17.6             | 17.9            | 20.6           |

\* Forsbeck and Luther, New England J. Med. 203: 1115-1121, 1930.  
† One in Tewksbury State Infirmary not added.

mission, Public Health in New York State, 1932. It will be seen from this that, as was pointed out by Godfrey, the higher case fatality in New York City has been largely due to the figures for 1916. When the figures for 1916 are omitted the case fatality for these years has been: New York City, 17 per cent; New York State, exclusive of the City, 16 per cent.

Forsbeck and Luther (F 57) have compared the case fatality rates in Massachusetts, 1916-1929, by certain population groups. It will be noticed that the case fatality has been highest in Boston, and over the mean in the group, under 2500 population.



No explanation of this higher fatality rate in the more densely populated centers has been encountered in the literature. Diagnosis and treatment are certainly as good, and reporting as complete. The chief reason for the difference is probably that in urban outbreaks the cases are more massed in the younger ages where the case fatality is highest. There is also the greater possibility of massive infection in cities.

**Other Factors Influencing Case Fatalities.** The possibility that sex, race and latitude may influence case fatality has been considered under the sections on these subjects.

**Fatality Trends.** Forsbeck and Luther (F 57) say that in Massachusetts, the fatality rate has been declining since 1911. They attribute this decline to (1) better diagnosing, (2) better reporting, (3) better treatment, (4) milder disease, (5) any combination of these.

There seems also to have been a somewhat lower case fatality in recent years in New York State. New York City, on the other hand, does not show such a tendency.

#### MULTIPLE CASES

##### DIFFICULTIES OF ESTIMATION

Before conclusions can be drawn as to the numbers of multiple cases that occur in any disease, it is essential to know just what are and what are not secondary cases. There are two factors that render this difficult in the case of poliomyelitis: (1) The confusion as to whether abortive cases should or should not be included. By abortive, we mean cases in which there is no evidence of invasion of the central nervous system, and which therefore cannot with certainty be diagnosed since the characteristic changes in the spinal fluid are not present. (2) The lack of agreement as to the incubation period of poliomyelitis, which complicates the decision as to which cases are infected from a common source, which from independent sources, and which are true secondary.

(1) **The Question of Inclusion of Abortive Cases.** It is to be expected that in a disease so protean in its manifestations as poliomyelitis, so exceptional in the experience of most physicians, and for which there is no simple diagnostic test, the difficulties of diagnosis would introduce into its statistical study a considerable error. The question of the inclusion or non-inclusion of the nonparalytic and abortive cases adds complexity to almost all phases of the statistics of poliomyelitis, but nowhere is this so evident as it is in an estimation of multiple cases of the disease, in which the diagnosis is frequently made primarily upon association with a paralytic case.

(2) **The Question as to Which Are True Secondary Cases.** Whether or not abortive cases are included, lack of definite knowledge as to the incubation period of poliomyelitis makes it a matter of conjecture as to which are true secondary cases, which have been infected from a common source, and which from an independent source. Aycock and Eaton (A 42) believe that the influence of a paralytic case upon the diagnosis of subsequent cases in a family decreases as time elapses from the appearance of the paralytic case; that is, if an indefinite illness occurs within a few days of a frank case of infantile paralysis in the same family the chances of its being called infantile paralysis are much greater than if it had occurred some weeks earlier or later than the paralyzed case. They collected a series of secondary cases, in which the information was available as to whether the cases were paralytic or abortive, and charted the time which elapsed between the primary and secondary case. The disproportionate grouping of the abortive cases near the primary case is clearly shown. It is apparent that the proportion of secondary abortive cases to secondary paralytic cases is highest on the day of the appearance of the first case, and that this proportion tends to diminish steadily. "For the first ten days from the appearance of the initial case, the proportion of abortive cases to paralyzed cases is 5 to 4, whereas for the remaining period, it is only 2 to 5. Inasmuch as there is no reason for supposing that this difference is due to any real difference in the behavior of the two types of the disease, we attribute it to the biased reporting of abortive cases, which has already been mentioned. Whether within the first few days of the occurrence of a paralyzed case other mild illnesses are incorrectly diagnosed as infantile paralysis, or a considerable number of actual abortive cases are missed, as the time interval increases, we do not attempt to say. In either case, the fact is apparent that the inclusion of abortive or suspicious cases introduces a gross error into the consideration of the time interval between the appearance of multiple cases." The paralyzed cases apparently arrange themselves into two groups. The first group extends from the date of the primary case to the eighth day following it, and comprises 80 per cent of the total paralyzed cases, while the second group, comprising 16 per cent, extends from the ninth or tenth day to the seventeenth day following the initial case, averaging 14 days.

The authors explain the two groups as representing a different source of infection, the earlier group arising from a common source, the later group being probably true secondary cases. From the time interval between the second group and the primary case, they conclude that the



TABLE 34  
INFANTILE PARALYSIS, SECONDARY CASES BY INTERVALS FROM INITIAL CASES IN SAME FAMILY\*

|                          | INTERVAL IN DAYS |    |    |    |    |    |    |    |    |                       |    |    |    |                        |    |    |    |    |    |    |                        |    |    |    |    |    |  |  |  |
|--------------------------|------------------|----|----|----|----|----|----|----|----|-----------------------|----|----|----|------------------------|----|----|----|----|----|----|------------------------|----|----|----|----|----|--|--|--|
|                          | 0                | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9                     | 10 | 11 | 12 | 13                     | 14 | 15 | 16 | 17 | 18 | 19 | 20                     | 21 | 22 | 23 | 24 | 25 |  |  |  |
| Sweden, 1905.....        | 12               | 22 | 15 | 14 | 11 | 7  | 9  | 7  | 5  | 5                     | 5  | 1  | 2  | Over 12 days, 12 cases |    |    |    |    |    |    |                        |    |    |    |    |    |  |  |  |
| New York City, 1916..... | 61               | 45 | 47 | 41 | 46 | 45 | 26 | 17 | 22 | 9                     | 8  | 7  | 3  | 3                      | 2  | 1  | 3  | 3  | 2  | 1  | Over 20 days, 15 cases |    |    |    |    |    |  |  |  |
| Massachusetts, 1916..... | 10               | 21 | 18 | 20 | 12 | 14 | 16 | 14 | 13 | Over 8 days, 54 cases |    |    |    |                        |    |    |    |    |    |    |                        |    |    |    |    |    |  |  |  |
| Aycock and Eaton series: |                  |    |    |    |    |    |    |    |    |                       |    |    |    |                        |    |    |    |    |    |    |                        |    |    |    |    |    |  |  |  |
| Total.....               | 40               | 46 | 34 | 29 | 28 | 19 | 23 | 27 | 15 | 6                     | 2  | 4  | 5  | 4                      | 4  | 6  | 4  | 1  | 0  | 1  | 0                      | 2  | 1  | 0  | 3  | 1  |  |  |  |
| Paralyzed.....           | 9                | 17 | 17 | 12 | 14 | 8  | 10 | 15 | 10 | 1                     | 1  | 3  | 4  | 2                      | 3  | 3  | 3  | 1  | 0  | 1  | 0                      | 2  | 1  | 0  | 2  | 1  |  |  |  |
| Abortive.....            | 31               | 29 | 17 | 17 | 14 | 11 | 13 | 12 | 5  | 5                     | 1  | 1  | 1  | 2                      | 1  | 3  | 1  | 0  | 0  | 0  | 0                      | 0  | 0  | 0  | 1  | 0  |  |  |  |

\* Aycock and Eaton, Am. J. Hyg. 5: 724, 1925.

TABLE 35

POLIOMYELITIS, DIPHTHERIA, AND SCARLET FEVER, INTERVAL BETWEEN INITIAL AND SUBSEQUENT CASES IN THE SAME FAMILY;  
NUMBER AND PER CENT OF CASES DEVELOPING AT DESIGNATED INTERVALS AFTER THE INITIAL CASE\*

|                                                                                                     | DAYS |      |      |      |      |      |     |     |       |       |       |     |
|-----------------------------------------------------------------------------------------------------|------|------|------|------|------|------|-----|-----|-------|-------|-------|-----|
|                                                                                                     | 0    | 1    | 2    | 3    | 4    | 5    | 6   | 7   | 8     | 9     | 10    | 11  |
| Lavinder, Freeman and Frost (Public Health Bull. 91:<br>129), Poliomyelitis in New York City, 1916: |      |      |      |      |      |      |     |     |       |       |       |     |
| Number.....                                                                                         | 61   | 45   | 47   | 41   | 46   | 45   | 26  | 17  | 22    | 9     | 8     | 7   |
| Per cent.....                                                                                       | 15.0 | 11.1 | 11.6 | 10.1 | 11.3 | 11.1 | 6.4 | 4.2 | 5.4   | 2.2   | 2.0   | 1.7 |
| Chapin, Diphtheria, Providence, Rhode Island, 1904-<br>1913:                                        |      |      |      |      |      |      |     |     |       |       |       |     |
| Number.....                                                                                         | 77   | 135  | 144  | 120  | 110  | 117  | 116 | 109 | 60    | 57    | 65    | 39  |
| Per cent.....                                                                                       | 4.5  | 8.0  | 8.5  | 7.1  | 6.5  | 6.9  | 6.8 | 6.4 | 3.5   | 3.4   | 3.8   | 2.3 |
| Chapin, Scarlet Fever, Providence, Rhode Island, 1904-<br>1913:                                     |      |      |      |      |      |      |     |     |       |       |       |     |
| Number.....                                                                                         | 100  | 162  | 146  | 118  | 127  | 126  | 81  | 105 | 72    | 75    | 57    | 56  |
| Per cent.....                                                                                       | 5.2  | 8.4  | 7.6  | 6.1  | 6.6  | 6.5  | 4.2 | 5.4 | 3.7   | 3.9   | 3.0   | 2.9 |
|                                                                                                     | 12   | 13   | 14   | 15   | 16   | 17   | 18  | 19  | 20-29 | 30-39 | 40-49 | 50+ |
| Lavinder, Freeman and Frost (Public Health Bull. 91:<br>129), Poliomyelitis in New York City, 1916: |      |      |      |      |      |      |     |     |       |       |       |     |
| Number.....                                                                                         | 3    | 3    | 2    | 1    | 3    | 3    | 2   | 1   | 3     | 8     | 2     | 2   |
| Per cent.....                                                                                       | 0.7  | 0.7  | 0.5  | 0.2  | 0.7  | 0.7  | 0.5 | 0.2 | 0.7   | 2.2   | 0.5   | 0.4 |
| Chapin, Diphtheria, Providence, Rhode Island, 1904-<br>1913:                                        |      |      |      |      |      |      |     |     |       |       |       |     |
| Number.....                                                                                         | 37   | 32   | 40   | 22   | 18   | 32   | 29  | 20  | 168   | 70    | 25    | 57  |
| Per cent.....                                                                                       | 2.1  | 1.9  | 2.4  | 1.3  | 1.1  | 1.9  | 1.7 | 1.2 | 9.9   | 4.1   | 1.5   | 3.3 |
| Chapin, Scarlet Fever, Providence, Rhode Island, 1904-<br>1913:                                     |      |      |      |      |      |      |     |     |       |       |       |     |
| Number.....                                                                                         | 42   | 57   | 51   | 46   | 31   | 32   | 36  | 24  | 163   | 72    | 63    | 91  |
| Per cent.....                                                                                       | 2.2  | 3.0  | 2.6  | 2.4  | 1.6  | 1.8  | 1.9 | 1.2 | 8.7   | 3.7   | 3.3   | 4.6 |

\* Data from Lavinder, Freeman and Frost, Public Health Bulletin, 91, 1918.



incubation period is 10 to 18 days, averaging 14 days. Table 34 collected from various sources by the same authors, gives the interval in days between primary and subsequent cases in families.

Lavinder, Freeman and Frost (L 16) have compared the time interval between multiple cases of poliomyelitis, diphtheria, and scarlet fever.

It will be seen from Table 35 which shows the number of days subsequent to the primary case that secondary cases developed, that in poliomyelitis the per cent is much higher early and stays higher until about the sixth day, when it falls abruptly well below that for the other two diseases.

The inference drawn by the authors from this is that true secondary cases constitute a much larger percentage of the multiple cases in scarlet fever and diphtheria, while common source cases constitute a larger percentage in poliomyelitis. This lends corroboration to the idea that while there is some menace in the family group, it is not so much the case itself as the source from which the case was infected, which in turn suggests that carriers play a much larger part in the spread of poliomyelitis than of the other two diseases.

In comparing multiple cases of poliomyelitis with those of scarlet fever and diphtheria, we must also remember that the ages affected in poliomyelitis are lower than for these other diseases, presumably due to an immunity or resistance developed relatively earlier. The chances that there would be more than one member of a family susceptible to poliomyelitis would be very much less than that there would be more than one member susceptible to these other diseases.

Aycock and Eaton (A 43) made a comparison between multiple cases of measles, scarlet fever, and poliomyelitis. They consider that the evidence shows that measles and scarlet fever are introduced into the family group by the initial case from which, after the onset of the disease, the infection is transmitted to other members of the family. Second and third cases occur as a rule simultaneously in measles; in scarlet fever there is a relatively large number of late secondary cases, probably due to a prolonged period of infectivity.

"Infantile paralysis, when introduced into a family, acts differently from measles or scarlet fever. Only exceptionally do multiple cases occur. When multiple cases do occur, they usually come down within a short time of each other, indicating simultaneous infection. In this respect, multiple cases of infantile paralysis resemble second and third cases of measles. This indicates that contact infection during the acute stage does not play the same rôle in this disease as in measles or scarlet

fever, but that the virus of infantile paralysis enters the family in such a way that in the few instances where more than one member is infected, this is accomplished practically simultaneously."

Since information is seldom given concerning the interval between primary and secondary cases, in the following consideration, the words "secondary cases" are used merely in the sense of subsequent cases.

#### ESTIMATIONS OF MULTIPLE CASES

There are several methods in general use for estimating multiple cases:

(1) The ratio of secondary to primary cases.

(2) The method of Chapin, which is to ascertain the total number of members of affected families residing at home, to subtract one member from each family to represent the primary case, and to regard all the remaining members as exposed. The proportion of the exposed who develop the disease, the "attack rate," is taken as an index of relative contagiousness.

(3) A more significant method is to use the second method, counting only those members of the family susceptible to the disease.

(1) **The Ratio of Secondary to Primary Cases.** The relative frequency with which initial and subsequent cases in families have occurred in various epidemics is summarized in Table 36.

(2) **The Method of Chapin.** The percentage of exposed persons in affected families who subsequently developed the disease has been studied in a few epidemics. Concerning the family incidence in the New York City epidemic of 1907, Emerson (N 20) says that of 2000 children in 762 families reported as exposed to the infection, there were 18 instances of 2 cases to a family, and 2 instances of 3 cases to a family. In "very few instances" were there more than 3.

Lavinder, Freeman and Frost (L 16) made the most careful study of attack rates among exposed members of families with poliomyelitis that has been made. They have added for the sake of comparison, similar figures of Chapin for scarlet fever and diphtheria. Table 37 summarizes the attack rates for the three diseases.

"The percentage of persons attacked at all ages, as shown by the table, is, for primary cases, almost the same. This is to be expected since, considering only one case to a family, the percentage attacked varies only with the average size of the family. The primary attack rates, in general, reflect only the selective age incidence of the disease. The secondary attack rates, however, would seem to indicate quite



striking differences in the liability of persons exposed in the family with a case of the disease to contract it. In poliomyelitis only one

TABLE 36  
RELATIVE FREQUENCY WITH WHICH SINGLE AND MULTIPLE CASES IN FAMILIES  
HAVE OCCURRED IN VARIOUS OUTBREAKS OF POLIOMYELITIS

| AUTHOR                                  | REFER-<br>ENCE | EPIDEMIC                          | TOTAL<br>FAMILIES | FAMILIES WITH |         |         |         |        | PER CENT<br>WITH 1<br>CASE |
|-----------------------------------------|----------------|-----------------------------------|-------------------|---------------|---------|---------|---------|--------|----------------------------|
|                                         |                |                                   |                   | 1 case        | 2 cases | 3 cases | 4 cases | Over 4 |                            |
| Lavinder, Free-<br>man and Frost        | L 16           | New York City, 1916               | 8,709             | 8,331         | 353     | 21      | 4       | —      | 95.6                       |
| Lavinder, Free-<br>man and Frost        | L 16           | 3 counties in New<br>Jersey, 1916 | 328               | 297           | 23      | 8       | —       | —      | 90.5                       |
| Francis                                 | F 59           | Texarkana, 1913                   | 143               | 139           | 3       | 1       | —       | —      | 97.2                       |
| Wickman                                 | W 21           | Sweden, 1905                      | 783               | 627           | 95      | 39      | 14      | 8      | 80.0                       |
| MacNalty                                | M 9            | Esher district, 1917              | 27                | 15            | 10      | 2       | —       | —      | 55.5                       |
| Shidler                                 | S 40           | Nebraska, 1910                    | 40                | 25            | 6       | 5       | 3       | 1      | 62.5                       |
|                                         | E 6            | Baden, 1930                       | 71                | 71            | —       | —       | —       | —      | 100.0                      |
| Dubois                                  | D 22           | Zürich, 1909-1921                 | 392               | 356           | 28      | 8       | —       | —      | 90.8                       |
| Hill                                    | H 22           | Minnesota, 1909                   | 292               | 257           | 30      | 4       | 1       | —      | 88.0                       |
| New York City<br>Health Depart-<br>ment | N 22           | New York City, 1931               | 3,999             | 3,901         | 95      | 3       | —       | —      | 97.5                       |

TABLE 37  
ATTACK RATES, PRIMARY AND SECONDARY: POLIOMYELITIS, NEW YORK CITY,  
1916, IN 8,709 FAMILIES; SCARLET FEVER, 1904-1909, IN 2,063 FAMILIES; AND  
DIPHThERIA, 1904-1913, IN 3,078 FAMILIES. PROVIDENCE, RHODE ISLAND,  
(CHAPIN)\*

| AGE                 | POLIOMYELITIS |                | SCARLET FEVER |                | DIPHThERIA |                |
|---------------------|---------------|----------------|---------------|----------------|------------|----------------|
|                     | Primary       | Second-<br>ary | Primary       | Second-<br>ary | Primary    | Second-<br>ary |
| 0 to 5 years.....   | 41.2          | 3.2            | 33.0          | 24.1           | 35.7       | 14.9           |
| 6 to 10 years.....  | 16.1          | 1.3            | 43.4          | 25.7           | 44.2       | 15.5           |
| 11 to 20 years..... | 4.0           | 0.20           | 20.2          | 9.7            | 19.2       | 6.9            |
| Over 20 years.....  | 0.6           | 0.02           | 2.9           | 1.2            | 3.8        | 1.8            |
| All ages.....       | 18.9          | 1.1            | 19.9          | 9.9            | 18.9       | 6.1            |

\* Lavinder, Freeman and Frost, Public Health Bulletin, 91, 1918.

person in a hundred exposed in the family with a case develops it, while in scarlet fever 1 in 10, and in diphtheria 1 in 16, of those exposed

develops the disease. This difference in the apparent contagiousness of the diseases is seen at all ages. It is more marked, however, at the higher ages. This is, of course, in part explained by the fact that only frank cases of poliomyelitis are included in the tabulation, although abortive and unrecognizable forms of the disease are apparently present in such families with frequency.

“In addition, the incidence of the disease in those exposed to infection from a previous case in the same family has been compared with the incidence in those of comparable ages in the general population.”

TABLE 38

COMPARATIVE INCIDENCE OF POLIOMYELITIS, SCARLET FEVER, AND DIPHTHERIA IN PERSONS EXPOSED IN THE GENERAL POPULATION AND IN PERSONS EXPOSED IN THE FAMILY WITH A CASE OF THE DISEASE (RATE PER 10,000)\*

| AGE                 | POLIOMYELITIS,<br>NEW YORK CITY,<br>1916 |                                       | SCARLET FEVER,<br>PROVIDENCE, R. I.,<br>1909-1911 |                                       | DIPHTHERIA,<br>PROVIDENCE, R. I.,<br>1909-1911 |                                       |
|---------------------|------------------------------------------|---------------------------------------|---------------------------------------------------|---------------------------------------|------------------------------------------------|---------------------------------------|
|                     | Incidence                                |                                       |                                                   |                                       |                                                |                                       |
|                     | In<br>general<br>popula-<br>tion         | In<br>persons<br>exposed<br>in family | In<br>general<br>popula-<br>tion                  | In<br>persons<br>exposed<br>in family | In<br>general<br>popula-<br>tion               | In<br>persons<br>exposed<br>in family |
| 0 to 5 years.....   | 124.5                                    | 318.0                                 | 93.1                                              | 2,410                                 | 111.1                                          | 1,490                                 |
| 6 to 10 years.....  | 20.8                                     | 127.0                                 | 115.0                                             | 2,570                                 | 97.0                                           | 1,550                                 |
| 11 to 20 years..... | 2.3                                      | 20.0                                  | 24.8                                              | 970                                   | 24.7                                           | 690                                   |
| Over 20 years.....  | 0.4                                      | 2.0                                   | 3.2                                               | 120                                   | 5.2                                            | 180                                   |
| All ages.....       | 17.9                                     | 109.0                                 | 26.5                                              | 990                                   | 28.2                                           | 610                                   |

\* Lavinder, Freeman and Frost, Public Health Bulletin, 91, 1918.

The difference in incidence of the three diseases in the general population and in those exposed in the family with a case are summarized in Table 38. From the summary in Table 38, it will be seen that those in the immediate environment of a case of poliomyelitis suffer from a much higher rate of incidence (approximately 6 times as great) than does the general population. The difference is greatest at the ages between 11 and 20.

“In scarlet fever and diphtheria, however, the increased liability to infection of those in the family with a case is much more striking. In scarlet fever the incidence among those in the family with a case is thirty-seven times as great as in the general population; in diphtheria twenty-two times as great.”



The authors call attention to the fact that the figures for scarlet fever and diphtheria refer to cases in which the patient remained at

TABLE 39  
INTENSIVE STUDIES OUTSIDE OF NEW YORK CITY: FAMILY SUMMARY SHOWING  
PRIMARY AND SUBSEQUENT CASES—PARALYTIC, ABORTIVE AND SUSPICIOUS  
CASES INCLUDED\*

| AGE                 | NUMBER<br>OF<br>PRIMARY<br>CASES | TOTAL<br>PERSONS IN<br>FAMILIES<br>INVOLVED | NUMBER OF<br>PERSONS<br>EXPOSED<br>AT AGE<br>INDICATED | SECONDARY CASES |             |
|---------------------|----------------------------------|---------------------------------------------|--------------------------------------------------------|-----------------|-------------|
|                     |                                  |                                             |                                                        | Number          | Attack rate |
| All ages.....       | 335                              | 2,238                                       | 1,903                                                  | 62              | 3.2         |
| Under 1 year.....   | —                                | —                                           | 71                                                     | 5               | 7.04        |
| 1 to 5 years.....   | —                                | —                                           | 265                                                    | 35              | 13.2        |
| 6 to 10 years.....  | —                                | —                                           | 245                                                    | 11              | 4.4         |
| 11 to 15 years..... | —                                | —                                           | 173                                                    | 4               | 2.3         |
| 16 to 20 years..... | —                                | —                                           | 69                                                     | 0               | 0           |
| Over 20 years.....  | —                                | —                                           | 1,080                                                  | 7               | 0.64        |

\* Lavinder, Freeman and Frost, Public Health Bulletin, 91, 1918.

TABLE 40  
CRUDE ATTACK RATES (PARALYTIC CASES ONLY) IN POLIOMYELITIS, MINNESOTA,  
1909\*

| AGE                 | TOTAL PERSONS NOT<br>SICK IN AFFECTED<br>FAMILIES |             |       | TOTAL PERSONS<br>SICK IN AFFECTED<br>FAMILIES |             |       | CRUDE ATTACK<br>RATES |             |       |
|---------------------|---------------------------------------------------|-------------|-------|-----------------------------------------------|-------------|-------|-----------------------|-------------|-------|
|                     | Male                                              | Fe-<br>male | Total | Male                                          | Fe-<br>male | Total | Male                  | Fe-<br>male | Total |
| Not given.....      | 102                                               | 86          | 188   | 5                                             | 2           | 7     | —                     | —           | —     |
| Under 1 year.....   | 16                                                | 13          | 29    | 10                                            | 11          | 21    | 28                    | 37          | 34    |
| 1 to 5 years.....   | 83                                                | 74          | 157   | 92                                            | 66          | 158   | 42                    | 38          | 40    |
| 6 to 10 years.....  | 75                                                | 56          | 131   | 40                                            | 37          | 77    | 28                    | 32          | 30    |
| 11 to 15 years..... | 39                                                | 36          | 75    | 17                                            | 8           | 25    | 24                    | 15          | 20    |
| 16 to 20 years..... | 32                                                | 39          | 71    | 14                                            | 7           | 21    | 24                    | 12          | 18    |
| Adults.....         | 333                                               | 353         | 686   | 15                                            | 8           | 23    | 4.3                   | 2.2         | 3.3   |
| Total.....          | 680                                               | 657         | 1,337 | 193                                           | 139         | 333   | 22                    | 17          | 20    |

\* Hill, Trans. Sect. Prev. Med., A. M. A., 1910, p. 322.

home, while a large majority of the cases of poliomyelitis were removed to an isolation hospital. In view of the fact, however, that the second-

ary attack rate was about equal to that observed in epidemics where no such removal was practised, this removal would not appear to have had any considerable effect on the development of secondary cases. They conclude:

"It would appear, therefore, that in poliomyelitis the recognized case of the disease is relatively a far less important source of infection than in scarlet fever or diphtheria."

These same authors also made certain intensive studies outside of New York City during the 1916 epidemic. Their figures, including the abortive and suspicious (*i.e.* nonparalytic and abortive) cases are given in Table 39.

It will be noticed that the secondary attack rate is appreciably higher in these cases outside New York City than in the cases within New York City, as shown in Table 38. The attack rate among those exposed was 109 per 10,000 in New York City, and 320 per 10,000 outside the city.

Hill's (H 22) figures for the Minnesota outbreak in 1909 are somewhat higher, even though his estimates include paralytic cases only. These are given in Table 40. MacNalty (M 9) in his report on the Esher and vicinity epidemic gives a table of attack rates of members of invaded households according to age. The incidence of attack in these persons was 26 per cent.

**(3) Attack Rates among Susceptibles.** A more refined measure of the contagiousness of a disease is, as previously stated, the proportion of susceptibles, who, when exposed to a case, contract the disease. This method is often used in diphtheria when the ratio of secondary cases to the total Schick positives in infected families is figured.

A simple means of determining susceptibility to poliomyelitis is lacking, and more indirect means must be employed. Godfrey (personal communication) has suggested that an approximation to such an attack rate among susceptibles would be had in an attack rate among only those children in affected families who are younger than the primary case. Such a limitation would take account of the variable external factors governing acquired immunity, since it would seem probable that if an older child in a family were susceptible, his younger brothers and sisters would in the majority of cases be also. This is the situation usually encountered in diphtheria, where it is exceptional to find younger children in a family Schick-negative and older ones Schick-positive.

No direct estimates on this basis have been reported, and not many



figures are available as to the relative age of the patient and other children in the family.

Francis (F 59) says that in Texarkana and vicinity, in 1913, the number and age of children was learned in 82 families with 315 children. In 62 families the youngest child was attacked. In 14, it was the next to the youngest. In one instance, there were 3 cases in a family, in three instances there were 2.

Herrman (H 21) says that in the cases in 1916 of which he had notes (the number is not given), in 80 per cent the patient was the youngest child in the family.

We can, however, approach such an estimate indirectly by seeing whether the proportion of multiple cases varies directly with the factors which influence the age incidence. Since the age incidence is lower in urban than in rural outbreaks, the chance that there will be another susceptible in the family is lower, and we should expect a lower secondary attack rate; since the age incidence is lower in the Southern than in the Northern states, we should expect a lower secondary attack rate in the South.

#### MULTIPLE CASES AND SECONDARY ATTACK RATES IN URBAN AND RURAL OUTBREAKS

In Table 36, it was noticed that the percentage of multiple cases was relatively higher in rural than in urban outbreaks. The most obvious explanation of this fact was that the age incidence was higher in the former and that the probability of more than one susceptible in a family was greater in rural than in urban communities. Not much information on this point has been located, but a few instances bear out the inference.

Hardman and McKay (H 11) say of the secondary cases in Ontario during 1929 that 24 out of the 26 secondary cases occurred in rural areas, although the cases numbered 297 urban and 129 rural. Of the urban cases, 67.3 per cent were under 10, of the rural cases 52.4 per cent were under 10.

Wernstedt (W 14) compares the multiple cases in urban and rural sections of Sweden in the epidemic of 1911-1913. His figures are given in Table 42. He states that in the urban districts 73.8 per cent of the cases were under 10 years of age, while in the rural districts, only 56.3 per cent of the cases were under 10.

An apparent contradiction to the idea that multiple cases increase as the age incidence increases has been noted in the epidemics of 1916

and 1931 in New York City. Mention has been made elsewhere (see under *Recent Age Trends*) of the increased age of the cases in 1931 over 1916, and the general trend which has been noticed as to increased age

TABLE 41

ATTACK RATES, POLIOMYELITIS, BY AGE OF MEMBERS OF INVADDED HOUSEHOLDS,  
ESHER DISTRICT, 1917\*

| AGE                    | NUMBER OF<br>PERSONS AT<br>THAT AGE | NUMBER OF<br>PERSONS AT<br>THAT AGE WHO<br>SUFFERED<br>ATTACK | PERCENTAGE<br>ATTACKED |
|------------------------|-------------------------------------|---------------------------------------------------------------|------------------------|
| Under 1 year.....      | 4                                   | 0                                                             | 0                      |
| 1 to 2 years.....      | 2                                   | 2                                                             | 100.0                  |
| 2 to 3 years.....      | 5                                   | 2                                                             | 40.0                   |
| 3 to 4 years.....      | 9                                   | 7                                                             | 77.8                   |
| 4 to 5 years.....      | 10                                  | 10                                                            | 100.0                  |
| 5 to 6 years.....      | 9                                   | 6                                                             | 66.7                   |
| 6 to 7 years.....      | 8                                   | 4                                                             | 50.0                   |
| 7 to 8 years.....      | 3                                   | 1                                                             | 33.3                   |
| 8 to 9 years.....      | 6                                   | 1                                                             | 16.7                   |
| 9 to 10 years.....     | 3                                   | 2                                                             | 66.7                   |
| 10 to 11 years.....    | 1                                   | 0                                                             | 0                      |
| 11 to 12 years.....    | 6                                   | 1                                                             | 16.7                   |
| 12 to 13 years.....    | 1                                   | 1                                                             | 100.0                  |
| 13 to 14 years.....    | 5                                   | 2                                                             | 40.0                   |
| 14 to 15 years.....    | 0                                   | 0                                                             | 0                      |
| 15 to 20 years.....    | 9                                   | 2                                                             | 22.2                   |
| 20 to 25 years.....    | 5                                   | 0                                                             | 0                      |
| 25 to 30 years.....    | 19                                  | 0                                                             | 0                      |
| 30 to 50 years.....    | 49                                  | 1                                                             | 2.0                    |
| 50 years and over..... | 8                                   | 0                                                             | 0                      |
| Total.....             | 162                                 | 42                                                            | 25.9                   |

\* MacNalty, Great Britain, Loc. Gov. Bd. n.s. 120, 1918.

incidence in the United States in this period. In 1916, 79.2 per cent of the cases were under 5 years; in 1931, only 53.3 per cent were under 5 years. In spite of this fact, in 1916, multiple cases occurred in 4.3 per cent of the families attacked in New York City, while in 1931,



only 2.2 per cent of the families attacked had more than one case. (See Table 36.)

TABLE 42  
INCIDENCE OF PARALYZED CASES IN HOUSEHOLDS IN CITIES, TOWNS AND RURAL DISTRICTS IN SWEDEN, 1911-1913\*

|                                                            | HOUSEHOLDS WITH |     |    |    |   | TOTAL<br>CASES<br>OBSERVED | PER CENT<br>OF HOUSE-<br>HOLDS<br>WITH 1<br>CASE ONLY |
|------------------------------------------------------------|-----------------|-----|----|----|---|----------------------------|-------------------------------------------------------|
|                                                            | 1               | 2   | 3  | 4  | 5 |                            |                                                       |
|                                                            | PARALYZED CASES |     |    |    |   |                            |                                                       |
| Large cities (over 100,000 popula-<br>tion).....           | 394             | 16  | 2  | —  | — | 432                        | 91.2                                                  |
| Cities with population between<br>10,000 and 100,000 ..... | 423             | 16  | 4  | —  | — | 467                        | 90.7                                                  |
| Small cities, under 10,000 popula-<br>tion.....            | 660             | 45  | 3  | —  | — | 759                        | 86.9                                                  |
| Total, urban.....                                          | 1,477           | 77  | 9  | —  | — | 1,658                      | 89.1                                                  |
| Rural.....                                                 | 4,040           | 380 | 79 | 16 | 1 | 5,106                      | 79.1                                                  |

\* Wernstedt, *Ergeb. d. Inn. Med. u. Kinderh.*, 26: 248, 1924.

SECONDARY CASES IN INSTITUTIONS

**Hospitals.** Secondary cases among nurses and attendants, as well as among patients in hospitals, are so rare as to surround the few that have been reported with the suggestion of coincidental infection rather than true secondary cases. This is to be expected at the present time when precautions are taken against the spread of poliomyelitis as against other contagious diseases. On the other hand promiscuous spread was not noted before such precautions were taken. Batten, in the Lumleian Lectures, 1916 (B 7), says that after 30 years experience at the Great Ormond Street Hospital for Sick Children, London, where cases of poliomyelitis in the acute stage were frequently admitted to the general wards, he vouches for the fact that no secondary cases had ever occurred there.

Browning (B 35) likewise reports that at Kings County Hospital, Brooklyn, where prior to the 1916 epidemic, cases were scattered through a general ward and cared for in the same way as the other children, no new case of infection developed. The personal laundry and bedding of the patients were not specially handled.

Collier (W 2) in recounting a similar experience at St. George's Hospital, London, where in spite of the lack of any precautions, secondary cases had never occurred, concludes that poliomyelitis is a disease in which infection is spread by carriers only, including perhaps those in the incubational period of the disease, and that the chances of spread of infection decline rapidly with the development of the clinical disease.

Emerson, in his Monograph on the New York City epidemic of 1916 (N 20) says: "No attendant, physician, nurse, or domestic, and no patient admitted to any of the hospitals throughout the City, for other cause than poliomyelitis, during the epidemic, contracted poliomyelitis. This has been the almost universal experience in the past, and has often been brought forward as a proof of the non-communicable character of the disease. In the minds of those who have studied the disease in the field, this experience would rather indicate that the simple methods of ward cleanliness and the usual technique of personal care employed in hospitals suffices to prevent communication of the disease, and this opinion is borne out by the experience in institutions for children where similar simple measures prevented the spread of the disease. One of the field nurses of the Department engaged in daily house to house visits among the families where active cases were isolated developed poliomyelitis in a severe paralytic form."

Other cases are from time to time reported in nurses. Josefson (J 13) reported that in the Swedish epidemic of 1911, 1 nurse became infected, and in the epidemic in Christiania in the same year 2 such infections occurred.

Aycock (A 38) encountered 3 cases among nurses in Massachusetts in 1927. There were 1189 cases in Massachusetts in 1927; nursing them were probably not more than 200 or 300 nurses. This would constitute a very high attack rate.

Iancu and Dariu (I 1; quoted by Longhin and Aurian, L 68) report the occurrence of a hospital epidemic where a sick child who had come from an infected district had been the source of infection of a series of 8 cases, 4 paralytic and 4 abortive. The successive infections seemed to proceed from bed to adjacent bed.

**Schools and Other Institutions.** Poliomyelitis rarely causes institutional outbreaks. There seems to be a general belief that institutions and boarding schools enjoy a special immunity. We know of no statistical study of the subject, but such figures as we have seem to bear this out.

Frost (F 71) reported that in the Cincinnati epidemic of 1911, 1



case developed in a large orphan asylum, but was followed by no further cases.

The Mayor's Committee (N 19) reports that in New York City in 1916, 38 institutions had 13,000 children under their care. Two thousand others were boarded in houses under observation of the institutions. Among the 13,000 children in the institutions, 9 cases of poliomyelitis occurred (0.69 per 1000). Among the 2000 boarding-out children, 16 cases occurred (8.0 per 1000). The incidence in the city as a whole was 8.6 per 1000 for children under 10 (Lavinder, Freeman and Frost, L 16). The age of children in the institutions is not given. Comparison with children under 10 is given, therefore, merely for convenience.

A few instances are encountered of spread in institutions. Bloomberg and Barenberg (B 16) reported a small outbreak, 10 paralytic cases and a "certain number" of abortive cases, occurring in the Home for Hebrew Infants, New York City in July, 1923. There was no unusual prevalence at the time in the city as a whole, although later in the summer the incidence was well above normal expectancy. The ages of the children attacked ranged from 6 months to 2 years. The ages of children in the institution ranged from a few days to 5 years.

Under *Milk*, we have discussed an outbreak which occurred in Broadstairs, England, in 1926, reported by Aycock (A 33) in which 34 cases occurred in boys in private boarding schools. MacNalty (G 16a) called attention to the large percentage of cases of polioencephalitis in this epidemic.

Fairbrother and Brown (F 5) mention that in 1929 "a small outbreak of bulbar poliomyelitis occurred in a private boarding school at Sevenoaks."

#### CONTACT BETWEEN CASES

##### DIRECT CONTACT

The lack of obvious connection between cases of poliomyelitis is one of the striking and constant features of the epidemiology of the disease. In only a small percentage of cases is it usually possible to obtain a history of exposure to a case, and while connected cases do occur, infection seems never to proceed regularly from cases to contacts in a well-defined series.

The complication which arises through inclusion or non-inclusion of abortive cases, the diagnosis of which often depends upon association with a frank case is discussed under multiple cases, and need only be

mentioned here. If such cases are included, the percentage of cases which give a history of contact is much increased.

Table 43, taken from the report of Lavinder, Freeman and Frost on the New York City epidemic of 1916, summarizes the effort to trace contact between 328 cases in the Borough of Richmond, where a de-

TABLE 43

BOROUGH OF RICHMOND, NEW YORK CITY, 1916: NUMBER AND PERCENTAGE OF ALL CASES OF POLIOMYELITIS, GIVING HISTORY OF RECENT CONTACT WITH A PREVIOUS CASE, ACUTE OR CONVALESCENT\*

| KINDS OF CONTACT                                   | PARALYZED CASES<br>SHOWING CONTACT | PER CENT OF ALL<br>PARALYZED CASES | ABORTIVE CASES<br>SHOWING CONTACT | PER CENT OF ALL<br>ABORTIVE CASES | SUSPICIOUS CASES<br>SHOWING CONTACT | PER CENT OF ALL<br>SUSPICIOUS CASES | TOTAL                          |                          |
|----------------------------------------------------|------------------------------------|------------------------------------|-----------------------------------|-----------------------------------|-------------------------------------|-------------------------------------|--------------------------------|--------------------------|
|                                                    |                                    |                                    |                                   |                                   |                                     |                                     | All cases show-<br>ing contact | Per cent of all<br>cases |
| Direct contact, positive:                          |                                    |                                    |                                   |                                   |                                     |                                     |                                |                          |
| (a) With paralytic case.....                       | 22                                 | 8.2                                | 5                                 | 20                                | 11                                  | 26.3                                | 38                             | 11.5                     |
| (b) With abortive case.....                        | 2                                  | 0.75                               | 0                                 | 0                                 | 1                                   | 2.6                                 | 3                              | 0.91                     |
| (c) With suspicious case.....                      | 18                                 | 6.8                                | 1                                 | 4.1                               | 2                                   | 5.2                                 | 21                             | 6.4                      |
| Direct contact, probable, with all<br>cases.....   | 6                                  | 2.3                                | 1                                 | 4.1                               | 1                                   | 2.6                                 | 8                              | 2.4                      |
| All direct contact.....                            | 48                                 | 18                                 | 7                                 | 29.1                              | 15                                  | 39.5                                | 70                             | 21.3                     |
| Indirect contact, positive:                        |                                    |                                    |                                   |                                   |                                     |                                     |                                |                          |
| (a) With paralytic cases.....                      | 4                                  | 1.5                                | 0                                 | 0                                 | 1                                   | 2.6                                 | 5                              | 1.5                      |
| (b) With abortive cases.....                       | 0                                  | 0                                  | 0                                 | 0                                 | 0                                   | 0                                   | 0                              | 0                        |
| (c) With suspicious cases.....                     | 1                                  | 0.37                               | 0                                 | 0                                 | 0                                   | 0                                   | 1                              | 0                        |
| Indirect contact, probable, with<br>all cases..... | 16                                 | 6                                  | 2                                 | 8.3                               | 2                                   | 5.2                                 | 20                             | 6.1                      |
| All indirect contact.....                          | 21                                 | 7.8                                | 2                                 | 8.3                               | 3                                   | 7.8                                 | 26                             | 7.6                      |
| Total, all contact.....                            | 69                                 | 25.9                               | 9                                 | 37.4                              | 18                                  | 47.3                                | 96                             | 29.2                     |

Table based on: Paralyzed cases, 266; abortive cases, 24; suspicious cases, 38; total, 328.

\* Lavinder, Freeman and Frost, Public Health Bulletin, 91, 1918.

tailed study was made by the United States Public Health Service. They use the term "abortive" to mean what in this book we have designated "nonparalytic," and "suspicious" to mean what we have called "abortive."

The investigators of the Mayor's Committee (N 19) visited 5496



cases in New York City during the 1916 epidemic. They stated that 599, or 10.9 per cent, furnished evidence of personal contact with other cases. The same Committee report that in New Rochelle, a town suburban to New York City, 30 per cent of cases gave such evidence in the same epidemic. Nicoll (N 29) reported that in New York State (exclusive of the city) evidence of contact was found in 20.4 per cent of cases. Twelve per cent of these were associated with other cases in the same family.

In Brooklyn, during the 1931 epidemic, a careful investigation of the first 500 cases by the New York City Health Department (N 21) disclosed the fact that in 469 of these contact with another case could not be proved, *i.e.*, in only 6.2 per cent could cases be referred to previous cases.

Halliday (H 3) states that in the Glasgow epidemic in 1928, comprising 100 cases, in only two instances, or 2 per cent, was it possible to trace a direct association among cases.

While in the larger urban epidemics this lack of connection to former cases is the rule, there are reported from time to time small outbreaks of connected cases.

Frost (F 71) states that in Britt, Iowa, a small town of 1300 population, there were, in 1910, 23 cases. In all but 2 of the cases after the first, direct contact with previous definite or suspected cases could be ascertained. The brother of the first case had recently visited an infected area. Morales, in a small outbreak of 10 cases in Porto Rico in 1928 (M 44) was able to trace contact between cases in every instance.

Longhin and Aurian, during the Roumanian epidemic of 1927 (L 68), studied a rural district in Dambovitza as likely to lend itself to the tracing of origins of cases. They concluded that direct contagion from one patient to another is much more frequent than many authors at present believe. Leake, Bolten and Smith (L 20) made a thorough investigation of the possibilities for contact in the Elkins, West Virginia, outbreak of December, 1916. This outbreak of 70 cases in a population of 6000 occurred in winter, when communication between houses was less frequent and therefore better remembered, but even with the most painstaking investigation, contact with previous cases could be ascertained in only 26 per cent of the cases. Indirect contact occurred so frequently through parents or friends that analysis was impossible.

Nicoll (N 29) reported a group of contact cases which occurred in a rural section of Northern New York State. Chart IX shows the various modes of contact by which the disease was transmitted from the primary

CHART IX  
POLIOMYELITIS  
DEVELOPMENT OF A CONTACT GROUP OF CASES  
JEFFERSON COUNTY, NEW YORK, AUGUST, 1916

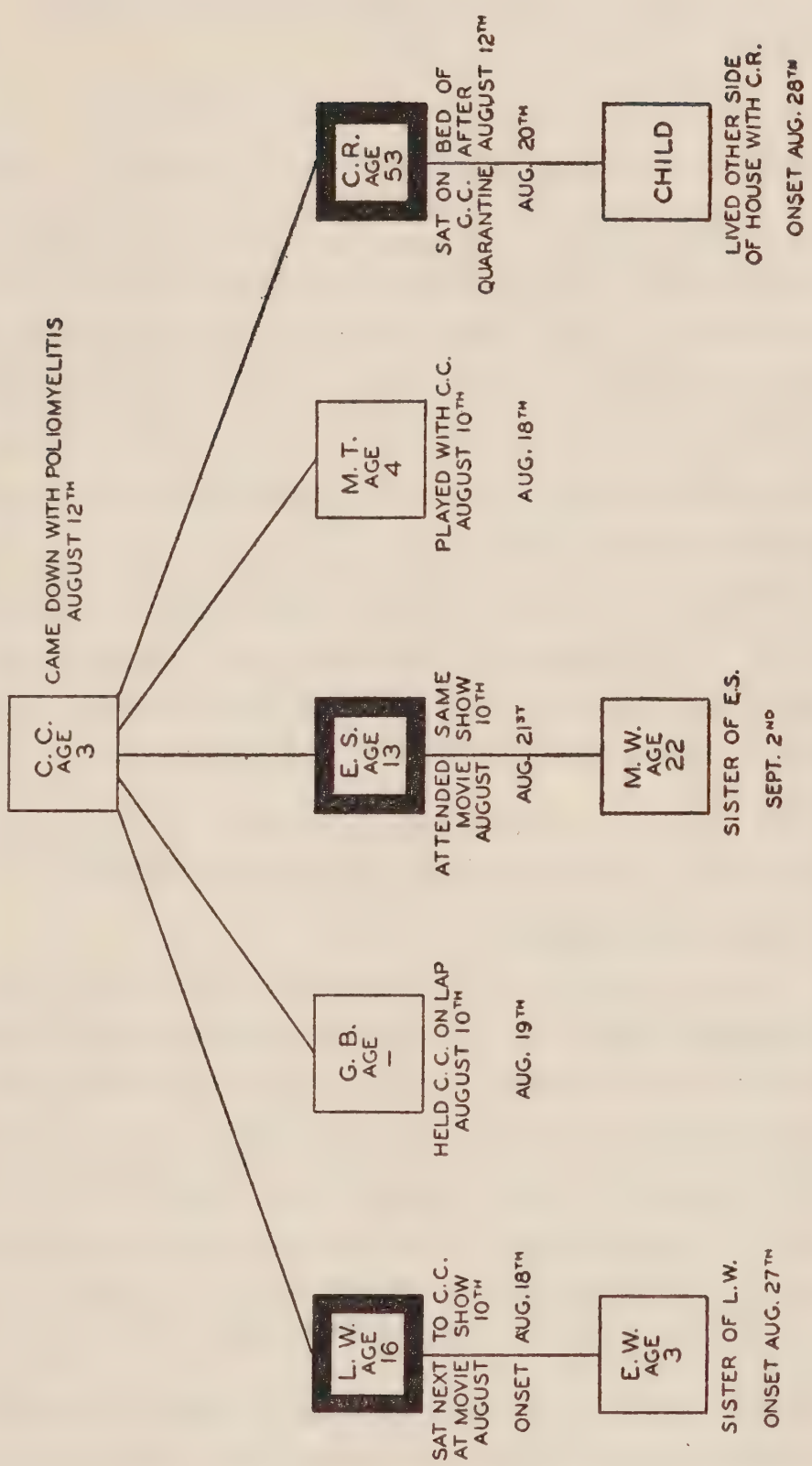


CHART IX. After Nicoll, Am. J. Dis. Child. 14: 69, 1917



case to 5 others, 3 of whom died, and from them to 3 others closely associated with them.

#### INDIRECT CONTACT—CARRIERS

From the preceding, therefore, it seems that in only a small percentage of cases of poliomyelitis can direct exposure to other cases be traced. Since in the contagious diseases, the percentage of instances in which contact between cases can be traced varies directly as the ratio of cases to carriers, this fact leads to one of two conclusions: either (1) the virus is transferred by agencies other than human beings, or (2) the clinically healthy carrier plays an extensive and important rôle in the transmission of the disease. In this chapter is considered only that evidence which bears upon the transfer of infection by persons, and the relation of carriers and cases.

A high carrier rate in a disease of low incidence is but another way of saying a widespread virus, which is either of low virulence, or is held in check by a high degree of host resistance. Although theoretically the validity of a widespread circulation of the virus should be experimentally demonstrable, such a demonstration has not, in point of fact, been accomplished.

Since negative results are rarely reported, it is impossible to form any opinion as to the proportion of failures and successes in such attempts.

#### Experimental Evidence

*Demonstration of the Virus.* To infect others, a person must not only harbor the virus, he must carry it in such a location that the transfer can be effected. Since such a transfer would be so easily accomplished by the nasopharyngeal secretions, the few instances in which the virus has been demonstrated in these secretions in human beings have been given possibly more weight than they numerically warrant. These results have, however, been reinforced by those in monkeys, where, regardless of the route of inoculation, the virus has been recovered from the nasopharyngeal secretions. (See under *Distribution of Virus*.)

Eight successful attempts have been made to demonstrate the virus in human beings. These are summarized below under *Period of Contagiousness*. These 8 instances, only 2 of which were in the secretions of clinically healthy persons, constitute, it is true, meager corroboration for the theory of a virus widely circulated by droplets of human secretions. This lack of positive evidence has not, however, been usually

interpreted as weighing heavily against such dissemination, since the technical difficulties attendant upon demonstration of the virus in dilute, filtered washings are very great. Not only is there no animal naturally susceptible to poliomyelitis, but there is also lacking a method of cultivating the virus artificially by which we may increase the dose obtained before injecting the animals.

*Neutralization Tests.* If power of neutralization by a person's serum is accepted as conclusive evidence of previous infection with the virus, no further proof is necessary to establish a high carrier rate, comparable to that of diphtheria. The available data on neutralization tests upon clinically healthy persons have been summarized under *The Host, Neutralization Tests*.

The validity of such an inference has recently, however, been challenged (see under *Immunity*), and the possibility has been suggested that this power may develop without contact with the virus. Until this problem is settled, it is debatable whether neutralization tests upon normal persons can be cited as proof of a high carrier rate.

*Skin Tests.* A method of testing for sensitization to the virus from previous exposure by intradermal tests has been sought, but is not yet available. (See under *Immunity*.)

### Epidemiological Evidence

*Direct and Indirect Contact.* Epidemiological evidence as to the rôle played by human carriers of the virus is more extensive and more convincing. In large cities or countrysides where communication has become extremely complex, satisfactory tracing of contacts is impossible. In more isolated localities, where people meet less often, the problem is easier.

It was in such a locality that Wickman (W 21) made his investigations. As Römer (R 25) points out, Wickman worked under conditions especially favorable for tracing contact. Sweden had compulsory notification. Further, the lonely parishes of Sweden with their isolated farms and houses made it possible to trace the spread of the disease under very simple conditions. Wickman was the first to recognize the great epidemiological importance of abortive cases and healthy carriers. In his reports of the 1905 and the 1911-1912 epidemics in Sweden, he cites very convincing instances where he could trace links of contact directly between cases, or indirectly through healthy intermediaries. Even under such simple conditions, Wickman was impressed with the fact that poliomyelitis seems more often to be propagated through the mediation of healthy carriers than from case to case.



Wickman's report of the spread of infection from a school in the little parish, of Trästena in 1905 has been widely quoted. Trästena, with somewhat more than 500 inhabitants, lies some distance from the high-road. The 102 houses were, almost without exception, each occupied by only one family, with its own water supply, its own cow, and its wants supplied by the products of its own farm. The only supplies which entered the parish came from a village where the disease was as yet unknown. In this parish, between June 28 and August 14, there occurred 49 cases of poliomyelitis, 26 of whom developed paralysis. Chart X shows the cases, with dates of onset. A search for the source of infection led to the public school. Many of the school children were themselves affected; other groups could be connected with the school, either by brothers or sisters who did attend, or through other intermediaries. The time of the appearance of the disease in the different families harmonized closely with the hypothesis of dissemination by way of the school. Where the disease originated from direct infection by sick school children the first cases appeared between June 28 and July 12. But where, in all probability, the infection was carried to a family by healthy school children, the first cases occurred between July 13 and 23. The school was closed on July 15.

Two of the Trästena school children were also believed by Wickman to be the source of infection for a small focus which developed in a little parish some hundred kilometers (about 60 miles) from Trästena. A boy, 3 years old, was the first victim. He travelled with his mother, on July 23, to a village, adjacent to Trästena, where his grandparents dwelt. The way led through infected districts; and while the child was at his grandparents' house, a relative came there who was employed as a servant on a farm where there were children ill. On July 27 the child was taken ill with the usual symptoms. On July 30, the mother set out with her sick child and on the same day arrived home. On August 17, the father of the boy was taken ill with paralysis in one leg. On August 15, a child living in their house was attacked. The next case occurred on August 21, about 1 kilometer from the infected house, and was followed, on August 27, by another in the immediate neighborhood. At the beginning of September the brother of the last patient was taken ill.

Leake, Bolten and Smith (L 20) in reporting the epidemic which occurred in Elkins, West Virginia, in the winter of 1916-1917, established contact in only 26 per cent of the cases. Indirect contact, through parents or acquaintances, occurred so frequently that analysis

SCHOOL EPIDEMIC, TRÄSTENA, SWEDEN, 1905

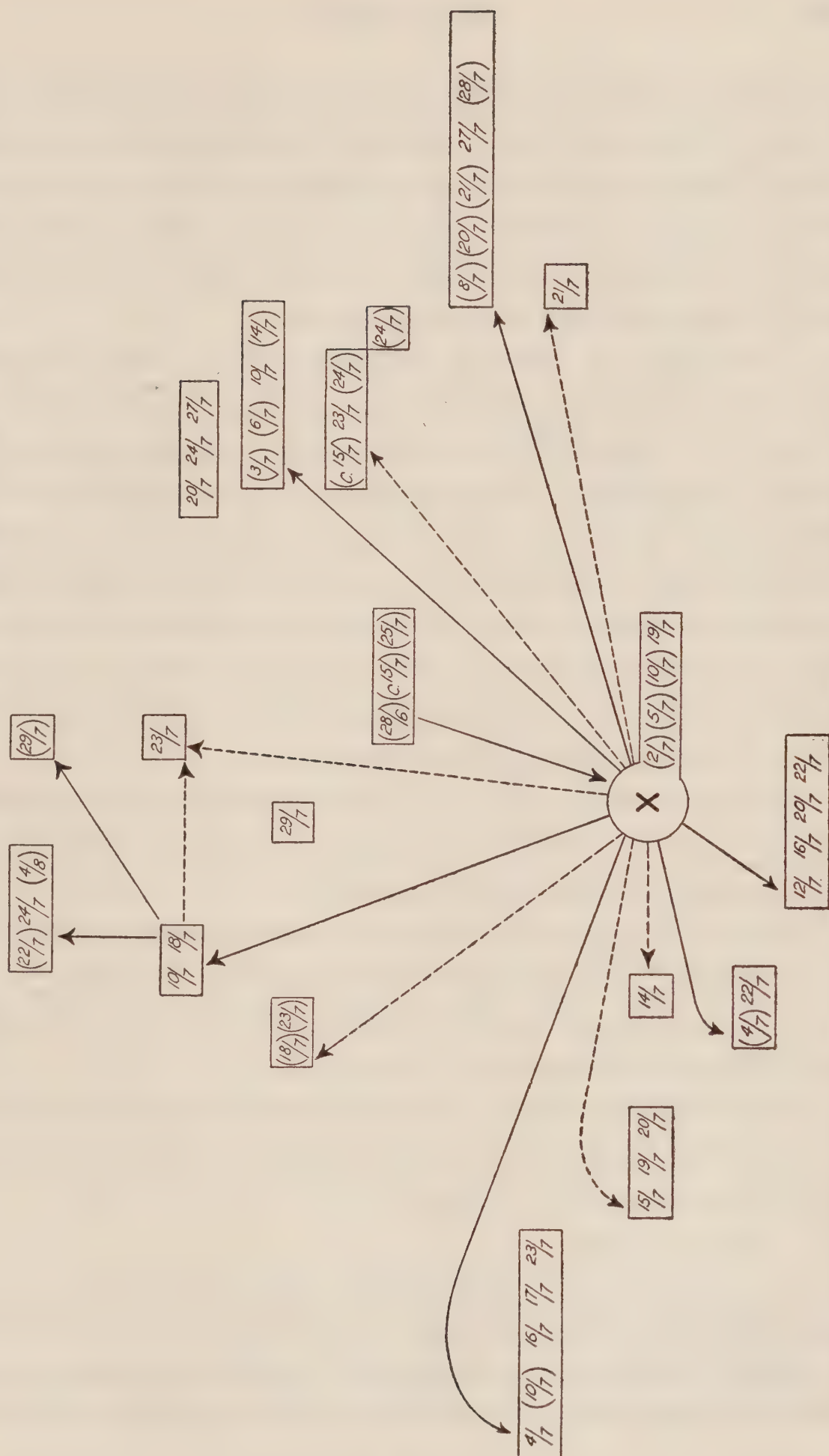


CHART X. Poliomyelitis, Träsfena, Sweden, 1905. The source of infection was believed to be the village school. Each paralogram represents a house, X, the school. The dates represent the onset of cases; those in parentheses, abortive cases. The continuous lines point to homes with school children, the broken lines to homes in which contact with the school through intermediaries was traced. (After Wickman, Nervous and Mental Diseases, Monograph Series, No. 16, 1913.)



was useless. It might be "that opportunities for direct infection presented themselves in Elkins which were not remarked by the parent, in stores, in street play, or at other times. In some of the rural cases studied, however, direct exposure to a recognized case of the disease could not have taken place. On account of the severe weather the children had been kept close at home for weeks, and no other member of the family had been sick." They add that in Elkins the usual history of indirect exposure was through an adult.

*Occupation of Heads of Families in Which Cases Occurred.* Mention is often made in outbreaks that the heads of families in which cases occurred were engaged in occupations which brought them in contact with large numbers of persons—clerks, salesmen, railway-employees. An example of this is cited by Hillenberg (H 23) who in his account of the 61 cases occurring in Halle in 1927, shows that the early cases occurred in widely separated portions of the city, and no contact could be established among them. One circumstance, however, seemed significant: in about one-third of the cases, the father of the affected child worked in Lenna (a neighboring village), and a smaller number of fathers were employed on the railroad. The author suggests the possibility that through the association of these men on the trip to and from Lenna, the virus might have been spread.

Longhin and Aurian (L 68) cite a similar instance in the Roumanian epidemic of 1927. A special train daily carried railroad employees to Bucharest from rural communities. These men apparently spread the disease widely from the Bucharest focus.

Wickman (W 21) mentions the fact that in the outbreak on the island of Borgö that the first cases appeared in the children of the only person who kept in active touch with the surrounding mainland, the father himself remaining well. No other means were found to account for the introduction of the disease onto the island.

**Period of Contagiousness.** The time during which a carrier, either active or passive, may pass on the infection to others is not known with certainty. The evidence which has been presented as to the period of contagiousness may be summarized:

*Active Carriage*

*During the Incubation Period.* In one experiment, Taylor and Amoss (T 1) recovered the virus from the nasopharyngeal washings of a paralytic case 5 days before the onset of symptoms.

Wilson (W 24) also says in this regard, "My own experience, in more than one family circle, has given me the impression that direct in-

fectivity is at its maximum during the incubation and preparalytic stage, and that once the virus has reached the nervous system, as revealed by the usual nervous symptoms, it ipso facto becomes tucked away, so to speak, in the deeper seated tissues of the individual concerned and is less communicable, he is less infective. If carriers are infective, as is allowed, they bear the virus in a state of activity, superficially, one might say, on their person, not in its recesses; hence the possibility of spread of contagion by means of droplets of virus-bearing mucus (as Dudley thinks) or otherwise." He also suggests that if further investigations substantiate this view, it may explain comfortably the fact that indiscriminate spread in hospitals never takes place, patients being usually in the paralytic stage on admission.

That cases may be infectious during either the incubation period or an early stage of their illness seems also to be shown by Knapp, Godfrey and Aycock (K 17) who reported an outbreak in which a milker who worked during his incubational period and the first 3 days of his illness, contaminated a milk supply from which 8 other cases were presumably infected.

*During the Acute Stage.* In a recent study, Paul and Trask (P 5) were able, in two out of twelve attempts, to demonstrate the virus in the oral secretions of cases of so-called abortive poliomyelitis. "None of these cases showed the usually accepted diagnostic criteria suggesting that meningitic or myelitic involvement was present. Ten of the cases came from families or communities in which contemporary cases of poliomyelitis existed. From two such examples of minor illness the virus of poliomyelitis was demonstrated. In both positive instances the material for inoculation was obtained within the first two days of minor illness; three other attempts to demonstrate the virus during these early stages (first two days) of illness, proved negative."

*During Convalescence.* In a nonparalytic case, Du Bois, Neal and Zingher (D 24) were able to demonstrate the virus 17 days after onset.

In an abortive case, Taylor and Amoss (T 1) demonstrated the virus in the secretions of a 10 year old boy, on the third day following the attack.

*Chronic Carriage.* Lucas and Osgood (L 73) reported the recovery of the virus from the nasopharyngeal secretions of a 5 year old boy, 4 months after a second attack. The child had a paralytic attack in February, 1910. In September, 1912, he had what was apparently a second attack with extension of the paralysis. Two weeks



after this, a 10 year old sister suffered an acute paralytic attack. On January 31, 1913, about 3 years after the first attack, and about 4 months after the second, the authors demonstrated the virus in the nasopharyngeal secretions.

This demonstration has been frequently cited as supporting the theory of chronic carriage of the virus. Such an inference seems, however, not warranted when we consider that second attacks are extremely rare, and the child, therefore, atypical. Also, the fact that at the time of his second attack, he infected his 10 year old sister, would seem to indicate a reinfection, since if the virus had been eliminated in an infectious state in the interval between the first and second attacks, a susceptible child would presumably have become infected earlier.

*Persistence of the Virus in the Tonsils, Pharyngeal Mucosa and Adenoids.* Flexner and Amoss (F 27) reported a series of tests with tonsils and pharyngeal mucosa removed at autopsy, and with tonsils and adenoids removed surgically at varying intervals after the acute attack. Their results indicate that the virus is regularly present in the nasopharynx of fatal cases during the acute stage. Corresponding tissues removed surgically at intervals varying from 8 to 150 days following the onset of the disease did not produce the typical experimental disease.

This series of tests reported by Flexner and Amoss with tonsils and adenoid tissue removed surgically at varying intervals after the acute stage, does not support the idea of chronic carriage.

*Persistence of the Virus in the Cord of Human Cases.* The cord of a patient removed  $3\frac{1}{2}$  months after the acute illness was shown by Krauspe (K 35) and Hässler (H 1) to contain the virus: A 14 year old boy had recovered from poliomyelitis; on the ninety-ninth day, pneumonia developed, and the child died in 24 hours. Sections showed old poliomyelitic foci and also quite recent alterations. An emulsion of the cord produced typical poliomyelitis in a monkey.

*Epidemiological Observations as to Chronic Carriage.* The observation which is discussed under *Periodicity*, that epidemics are more apt to recur in a place once the site of an epidemic than in a locality that has remained free, is suggestive of the persistence of chronic carriers. The instances in which cases occur in families after an interval of some years (see under *The Host, Inheritance Factor*) is also suggestive of a chronic carrier.

*Passive Carriage.* Passive carriage of the virus has been demonstrated in 2 instances, both times in pooled washings of healthy contacts of cases:

Flexner, Clark and Fraser (F 38) demonstrated the virus in the pooled secretions of the parents of a paralytic case 16 days after the onset of the child's illness.

Kling and Pettersson (K 15) recovered the virus in the pooled nasal washings of the wife and 3 children (10 to 14 years), 5 days after the onset and 1 day after the death of a patient. These authors had reported the recovery of the virus earlier from the pooled washings of contacts (W 14a), but the disease as reported in the monkey was not typical, and their earlier results have been questioned.

**Relative Infectiousness of Active and Passive Carriers.** The question as to whether contacts of more virulent viruses of poliomyelitis (as evidenced by fatal or severely paralyzed cases) show a larger percentage of cases than those of mild viruses (as evidenced by non-paralytic or abortive cases) has not been subjected to epidemiological study. In diphtheria, single cases are demonstrably more infectious than single carriers, even though the latter, by force of numbers, may be the more important factor. We have no evidence that this is the case in poliomyelitis. Stallybrass (S 53) says: "The severity of the disease is no indication of the numbers of micro-organisms discharged into the exterior. In poliomyelitis, the occurrence of actual disease, as opposed to an immunizing sub-infection, indicates the presence of the virus in the central nervous system and is no indication of the numbers of microbes released from the orifices, and there appears no reason why a case should be any more 'infectious' than a carrier; experience vindicates this belief. There is every reason to believe that in relation to the epidemic diseases of the central nervous system the carrier is the main agent in the dissemination of the virus. The relative importance of the clinical cases and of the temporary carriers depends not only upon their intrinsic infectiousness, but upon their relative frequency."

Collier (C 21; C 20) indeed advances the theory that case to case infection does not occur, and that all infection is through healthy carriers. He believes that when a person develops the disease, he ceases at once to be capable of transmitting the virus to others.

**Spread of Disease along Lines of Human Transportation.** In more densely populated localities, while it is impossible to trace, through the maze of human intercommunication, the spread of the disease from individual to individual, it has been instructive to follow the mass movements of the disease. In general, outbreaks of poliomyelitis spread along the lines of human transportation.

Leegaard (cited by Wickman, W 21) was the first to point out that



poliomyelitis showed a remarkable relation to highways, an observation that has been many times confirmed. He did not, however, argue from this that the spread is effected by human agencies. Wickman, however, drew this conclusion.

Lavinder, Freeman and Frost (L 16) say, concerning the spread of the disease from New York City in 1916, "Among the smaller units of population, those cities of largest size, situated on main lines of travel, were in general first attacked, the smaller cities, and those farther from main lines of travel, were attacked later. The disease seemed to spread primarily from city to city. The smaller communities and rural districts were apparently infected from the nearest large group of population. The influence of no factor of consequence other than the number and distribution of human population is discernible in the spread of the disease."

## PART II. EPIDEMIOLOGY OF THE HOST

Poliomyelitis has usually been considered by those attempting to integrate the facts bearing upon its mode of spread as a most contradictory disease. This seeming inconsistency forces insistently upon one the realization that he is dealing with not a simple but a compound phenomenon, with the epidemiology not of one but of two distinct conditions—that of the spread of the virus and that of the susceptibility of the host.

In the following pages we consider the epidemiology of the host, or that condition of the host which determines the outcome of infection. There is an increasing belief that persons who develop the disease rather than immunity when the virus is implanted in them, vary from the normal. That this factor of nonspecific susceptibility, which determines the population at risk, may have an epidemiology entirely distinct from the epidemiology of the spread of the infection, is a somewhat new idea. That the two may vary with totally unrelated factors seems, however, not at all unreasonable, nor that the complexity and seeming inconsistency of the spread of the disease may depend upon quantitative variations of the extent to which the two factors are at work.

Those factors with which susceptibility to poliomyelitis is known to vary are considered under the following headings: Age, Sex, Race, Constitutional Factors and Neutralization Tests upon the Sera of Normal Persons. The last is placed here for convenience and because of the epidemiological significance, though the inclusion is open to question.

## AGE INCIDENCE

**Virgin Soil Epidemics.** The first experience, or the experience after a long period of freedom, of a population with the virus of a disease is interesting in that there is brought to light any special susceptibility or lack of susceptibility, uninfluenced by acquired immunity, among different age groups. A familiar example of a virus striking root upon such virgin soil was the epidemic of measles which occurred upon the Faroe Islands in 1846.

Virgin soil epidemics occur inevitably in isolated communities, out of communication with the world, from which it follows that laboratory confirmation of the diagnosis will be impossible. The after effects of an epidemic of poliomyelitis are not, however, easily confused with other diseases.

Several such epidemics have been reported as poliomyelitis: one upon the island of Guam in 1899, reported by Grunwell (G 19); one upon the island of Nauru in 1910, reported by Müller (M 50); and one in New Guinea in 1929 (personal communication from Dr. Jean Macnamara). It is at least an interesting coincidence, and perhaps a significant one, that these three Pacific islands are relatively close together, and their inhabitants more or less closely related racially. The most characteristic feature of each epidemic, the inexplicable immunity enjoyed by the children, is also common to the three.

*Guam, 1899* (G 19). Poliomyelitis had been unknown in Guam, an island of the Ladrone group, until the arrival in May, 1899, of a Spanish transport. Within a week, the disease started, and spread over the entire island. Grunwell, a surgeon in the United States Navy, who reported the epidemic, arrived several months later, after the epidemic had died down, and he was dependent upon the statements of those who had passed through it for his information concerning the acute stage.

The number of cases could not be ascertained with accuracy. Grunwell states that there were 70 deaths and a "large number" of recoveries with paralysis.

*Age Incidence.* Young adults were the most frequent victims. Grunwell states clearly that the *extremes* of age in the cases observed were from 15 to 50 years.

*Nauru, 1910* (M 50). Nauru is an island in the Pacific Ocean, almost on the Equator, with a climate such as would be expected from the location. The population in 1910 consisted of about 1250 natives, 80 Europeans, and about 1000 adult laborers imported from China and



the Caroline Islands. The proportion of Chinese and Carolinians is not given.

In January, 1910, an epidemic started with a case in a laborer from the island of Ponape. Within a fortnight, there were attacked: 470 natives, 37 of whom died; 220 imported laborers from the Caroline Islands, 1 of whom died; and 2 Europeans, both of whom recovered. The Chinese were not affected.

Two boats had entered the harbor at Nauru, one from Australia, and one from Hongkong by way of the Caroline, Marshall, and Ellice Islands. Neither boat had illness aboard; the natives from these islands who came on the latter boat were well and remained so.

*Age Incidence.* Müller states that very few children below 12 years of age were affected, and no aged persons. The severest cases were under 40 years. Three nurslings and their mothers were affected. The preponderance of adults in the Nauru population, due to the imported adult laborers, has been mentioned. The native population had presumably a normal age distribution. Why the native children should have suffered so little is unknown.

Müller observes that among the Caroline Islanders all those affected were from the Island of Pingelap, although these comprised only 15 per cent of the Carolinians on Nauru. He states that these natives of Pingelap closely resembled the natives of Nauru who were so severely affected, both having a very marked tendency to obesity.

*Fatality.* Of 692 cases, 38 died, a case fatality of 5.4 per cent. This would be an extremely low case fatality for poliomyelitis in an epidemic affecting chiefly young children, in whom the fatality is consistently lower than in adults. In a "virgin soil," and among adults such a fatality throws some doubt upon the identity of the disease. In this connection, however, Dr. Jean Macnamara of Australia (personal communication) has told us that Dr. Ralph Allen had recently examined many of these 1910 cases on Nauru and considered that they manifested the typical deformities of neglected poliomyelitis.

*New Guinea.* There occurred in 1929 an epidemic of poliomyelitis in the British Solomon Islands and in New Guinea. Concerning the former, we have no direct information. The section of New Guinea affected was under the mandate of Australia, and the report of the Medical Officer in Charge has been sent to us by Dr. Jean Macnamara.

In June, 1929, word was received in New Guinea that a serious epidemic of poliomyelitis was occurring in the British Solomon Islands. In the latter part of August, the disease was first diagnosed in New

Guinea, although subsequent investigation established the fact that earlier cases had been overlooked.

Rabaul, New Guinea, has very infrequent direct communication with the Solomon Islands. Kieta, however, which lies between New Guinea and the Solomons, is in frequent communication with both. Although no cases developed in Kieta, the inference was drawn that infection reached New Guinea by way of Kieta.

The report of the Medical Officer emphasizes the fact that the disease had been sporadically present in the British Solomon Islands, and in the Morobe district (the mainland of New Guinea), and on the island of Manus. So far as was known, no previous cases had occurred in New Britain or in New Ireland. Both islands were, however, in frequent communication with the mainland of New Guinea. This area is therefore, rather questionably to be considered virgin soil, but we have included it here, partly because it has been so referred to in the literature, partly because of the age incidence, which was similar to the epidemics in Guam and Nauru, and the extremely high rate of attack in some sections.

*Diagnosis.* No autopsies, and therefore no laboratory confirmation, of the diagnosis were possible under the existing conditions. The clinical picture as given in the report is typical of poliomyelitis.

*Fatality.* The case fatality was extremely high. Of the 500 cases estimated to have occurred, approximately 190 died, a fatality of 38 per cent.

*Age Incidence.* The investigation of the epidemic revealed a relative immunity of the children. In New Ireland, of 138 cases, adults constituted 87 per cent, children 13 per cent; in Manus, of 184 cases, adults constituted 91 per cent, children 9 per cent.

There was, so far as is known, no disproportionate number of adults in the population. The rates, which are given for some of the villages in the Manus district, indicate a real difference in resistance between children and adults:

| <i>Village</i> | <i>Adult<br/>(Over Puberty)<br/>Cases per 100<br/>population</i> | <i>Children<br/>(Birth to Puberty)<br/>Cases per 100<br/>population</i> |
|----------------|------------------------------------------------------------------|-------------------------------------------------------------------------|
| Mokereng.....  | 15.3                                                             | 0                                                                       |
| Papitalai..... | 5.4                                                              | 0                                                                       |
| Loniu.....     | 6.1                                                              | 0.8                                                                     |
| Pak.....       | 5.8                                                              | 0                                                                       |
| Liap.....      | 16.3                                                             | 2.1                                                                     |



CHART XI



CHART XI. From Krahn, Arch. f. Hyg. 101: 65, 1929

Specific Morbidity Rates Adjusted to Age Groups. Poliomyelitis, as implied by the designation infantile paralysis, is typically a disease

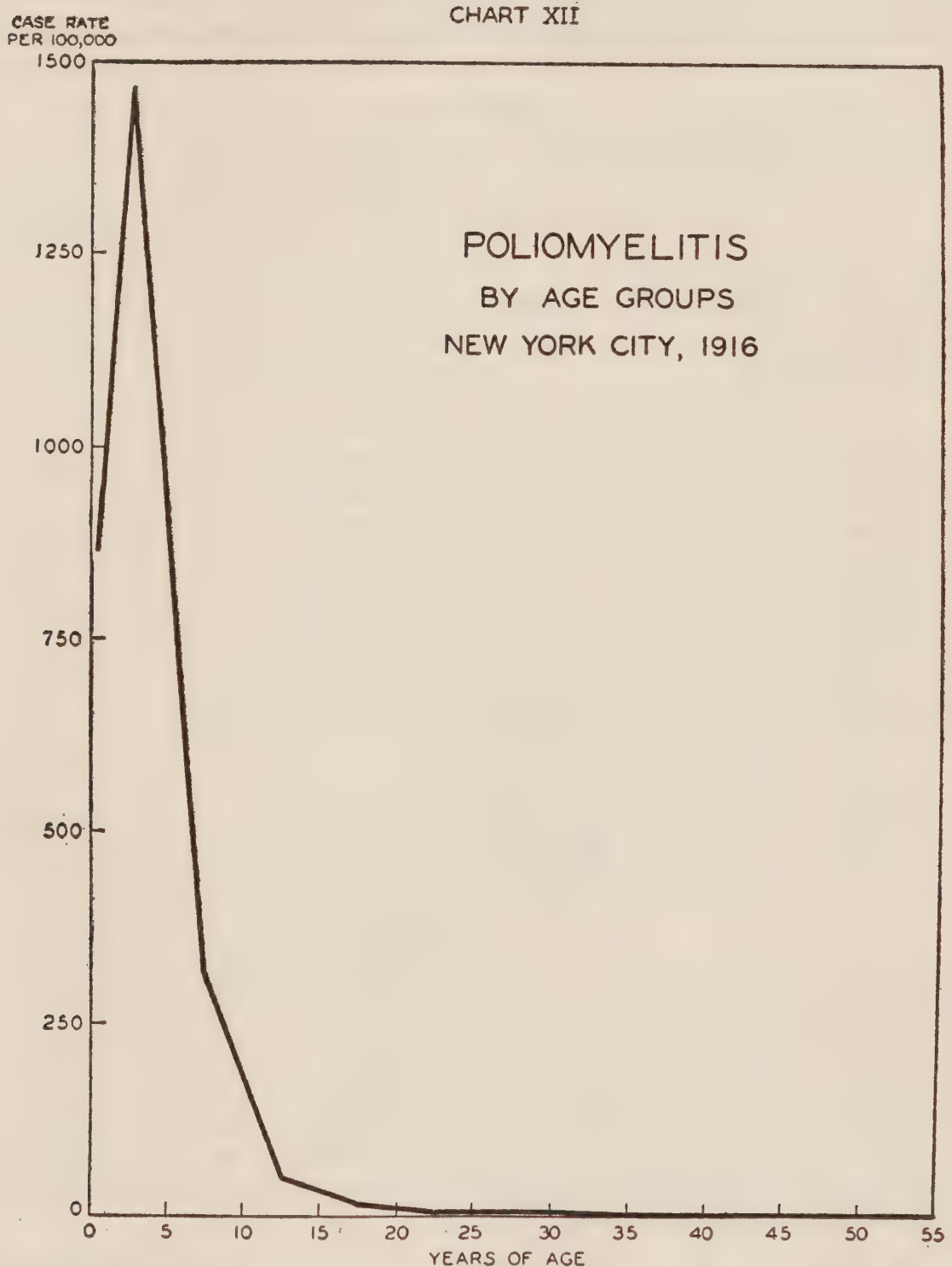


CHART XII. Figures from Lavinder, Freeman, and Frost, Public Health Bulletin 91, 1918.

of the early years of life. This highly disproportionate incidence of the disease in these age groups is apparent where the attack rates at the various ages are available.



Lavinder, Freeman and Frost (L 16) computed the attack rates at different ages for the New York City epidemic of 1916. Table 44 and Chart XII illustrate the highly selective action of the disease. In the ages between 1 and 4 approximately 1 out of 70 children was attacked,

TABLE 44  
ATTACK RATES AT DIFFERENT AGES, NEW YORK CITY, 1916\*

| AGE GROUPS               | ESTIMATED<br>PERSONS<br>LIVING AT<br>THAT AGE | CASES AT THAT<br>AGE | CASES<br>PER 100,000<br>PERSONS |
|--------------------------|-----------------------------------------------|----------------------|---------------------------------|
| Under 1 year.....        | 117,000                                       | 1,014                | 867                             |
| 1 to 4 years.....        | 422,900                                       | 6,217                | 1,469                           |
| Total under 5 years..... | 539,900                                       | 7,231                | 1,339                           |
| 5 to 9 years.....        | 469,800                                       | 1,483                | 316                             |
| 10 to 14 years.....      | 452,600                                       | 225                  | 49.7                            |
| 15 to 19 years.....      | 484,200                                       | 78                   | 16.1                            |
| 20 to 24 years.....      | 556,300                                       | 31                   | 5.6                             |
| 25 to 34 years.....      | 969,000                                       | 59                   | 6.1                             |
| 35 to 44 years.....      | 731,400                                       | 17                   | 2.3                             |
| 45 to 64 years.....      | 693,000                                       | 7                    | 1.0                             |
| 65 years and over.....   | 145,000                                       | 0                    | 0                               |

\* Lavinder, Freeman and Frost, Public Health Bulletin, 91, 1918.

TABLE 45  
POLIOMYELITIS, CINCINNATI, OHIO, 1910; INCIDENCE OF CASES PER 100,000 IN EACH AGE GROUP\*

| AGE                | NUMBER<br>OF PERSONS OF<br>THIS AGE<br>IN CINCINNATI,<br>1910 | POLIOMYELITIS, 1911 |                          |
|--------------------|---------------------------------------------------------------|---------------------|--------------------------|
|                    |                                                               | Number of<br>cases  | Incidence per<br>100,000 |
| Under 5 years..... | 29,172                                                        | 85                  | 291.4                    |
| 5 to 14 years..... | 55,825                                                        | 12                  | 21.5                     |
| Over 14 years..... | 278,594                                                       | 0                   | 0                        |
| All ages.....      | 363,591                                                       | 97                  | 26.5                     |

\* Frost, Hyg. Lab. Bull. No. 90, 1913.

while for the ages between 45 and 64 only 1 person out of 100,000 was attacked.

Frost (F 71) reports also the specific rates by age groups in the Cincinnati epidemic of 1911, showing the greatly disproportionate incidence

of poliomyelitis among children under 5 years. These are given in Table 45.

**Influence of Age upon Case Fatality.** The case fatality varies markedly for the various age groups, being almost invariably higher among infants under one year and among the older age groups, where the incidence is low, and lowest among the younger age groups where the incidence is highest. Why the older age groups should be better able to resist infection with the virus, but, once infected, should succumb more frequently, has not been explained.

This effect of age upon case fatality is considered under case fatality.

**Age Incidence and Population Density.** It has been many times observed that in outbreaks of poliomyelitis, the age incidence will vary with the concentration of population. The more densely populated the community, the younger will be the age of those affected.

This fact was, so far as we can determine, first pointed out by Frost in 1913 (Hyg. Lab. Bull. No. 90, 1913, pp. 209 and 251). Wernstedt in 1924 (Ergeb. d. Inn. Med. u. Kind. 26: 328, 1924) says that he first pointed this out. He quotes as reference his "first communication to the *Jahresbericht der Medizinalverwaltung* of 1911." We can find no reference to this publication. In his bibliography in the 1924 article he gives a 1911 reference: *Diskussion, Svenska läkars. förhandl.* 1911, p. 361, but on that page he speaks of the *general* incidence in city and country, and not of *age* incidence in city and country. Since in his report of 1912 to the Fifteenth International Congress of Hygiene and Demography (S 67) he again mentions the difference in general incidence, but not age incidence, it seems probable that the misunderstanding has arisen through confusion.

*Median Ages of Cases according to Density of Population.* Forsbeck and Luther (F 57) made a study of the age incidence of poliomyelitis according to the density of population in Massachusetts 1916-1929. Table 46 shows the median age in the nine density groups.

Compared with the median ages in Massachusetts, are the median ages for the various boroughs of New York City in the 1916 epidemic. In Table 47, we have given the median ages of the cases of poliomyelitis in 1916 for each borough, and, for comparison the number of persons per acre in that borough by the Census of 1910; similar figures for 1916 are not available. In order to compare the median ages of these New York cases with those in Massachusetts, given in Table 46, we have given also, in column five, the computed number of persons per square mile.



A further example of the variation in age incidence with the density of the population is given by Aycock (A 35) who tabulated the age incidence of 848 cases of poliomyelitis in Vermont, 1912-1925.

Nicoll (N 28) compared the age distribution of cases and deaths from poliomyelitis during the epidemic of 1916 in various sections of New

TABLE 46  
CASES OF ANTERIOR POLIOMYELITIS IN MASSACHUSETTS: MEDIAN AGE IN DENSITY GROUPS\*

| GROUP | DENSITY OF POPULATION PER<br>SQUARE MILE | MEDIAN AGE |
|-------|------------------------------------------|------------|
| 1     | 0-50                                     | 8.1        |
| 2     | 50-100                                   | 7.7        |
| 3     | 100-200                                  | 6.2        |
| 4     | 200-500                                  | 6.2        |
| 5     | 500-1,000                                | 6.0        |
| 6     | 1,000-2,000                              | 4.9        |
| 7     | 2,000-5,000                              | 5.3        |
| 8     | 5,000-10,000                             | 3.7        |
| 9     | 10,000-25,000                            | 4.5        |

\* Forsbeck and Luther, New England J. Med. 203: 1115, 1930.

TABLE 47  
MEDIAN AGES OF CASES DURING THE NEW YORK CITY EPIDEMIC OF 1916\*

| BOROUGH        | NUMBER OF<br>CASES | MEDIAN AGE | NUMBER OF<br>PERSONS PER<br>ACRE,<br>CENSUS OF<br>1910 | NUMBER OF<br>PERSONS PER<br>SQUARE MILE<br>COMPUTED<br>FROM PRECED-<br>ING COLUMN |
|----------------|--------------------|------------|--------------------------------------------------------|-----------------------------------------------------------------------------------|
| Manhattan..... | 2,591              | 1.6        | 176.0                                                  | 112,640                                                                           |
| Brooklyn.....  | 4,337              | 1.7        | 42.0                                                   | 26,880                                                                            |
| Bronx.....     | 672                | 2.1        | 16.0                                                   | 10,240                                                                            |
| Queens.....    | 1,237              | 2.2        | 3.5                                                    | 2,240                                                                             |
| Richmond.....  | 294                | 2.2        | 2.3                                                    | 1,472                                                                             |

\* Figures from the table of age incidence given by Lavinder, Freeman, and Frost, Public Health Bulletin, 91, 1918.

York State. In Table 49, he has compared the age groupings of cases and deaths in New York City, upstate cities, and rural New York. In the cases, and especially in the deaths, the lower age of the urban series is noted.

TABLE 48  
AGE DISTRIBUTION OF POLIOMYELITIS IN VERMONT, 1912-1925\*

| AGE GROUP              | CITIES, OVER<br>7,500 POPULATION |          | VILLAGES, 100-<br>7,500 POPULATION |          | COUNTRY,<br>ISOLATED FARMS |          |
|------------------------|----------------------------------|----------|------------------------------------|----------|----------------------------|----------|
|                        | Cases                            | Per cent | Cases                              | Per cent | Cases                      | Per cent |
| Under 5 years.....     | 122                              | 60.40    | 104                                | 36.20    | 99                         | 24.20    |
| 5 to 9 years.....      | 41                               | 20.85    | 86                                 | 30.80    | 102                        | 25.70    |
| 10 to 14 years.....    | 15                               | 7.80     | 30                                 | 11.30    | 73                         | 18.90    |
| 15 to 19 years.....    | 7                                | 4.05     | 25                                 | 10.10    | 49                         | 14.00    |
| 20 to 24 years.....    | 5                                | 3.23     | 7                                  | 3.16     | 19                         | 6.05     |
| 25 to 29 years.....    | 2                                | 1.35     | 8                                  | 3.80     | 14                         | 4.65     |
| 30 to 34 years.....    | 3                                | 2.18     | 4                                  | 2.05     | 12                         | 4.31     |
| 35 years and over..... | 1                                | 0.14     | 9                                  | 2.59     | 11                         | 2.19     |

\* Aycock, Am. J. Hyg. 8: 35, 1928.

TABLE 49  
AGE DISTRIBUTION OF CASES AND DEATHS FROM POLIOMYELITIS DURING THE  
EPIDEMIC OF 1916 IN DIFFERENT SECTIONS OF NEW YORK STATE\*

| AGE                                              | CASES                                  |          |                                           |          |                                           |          |
|--------------------------------------------------|----------------------------------------|----------|-------------------------------------------|----------|-------------------------------------------|----------|
|                                                  | New York City,<br>June-August,<br>1916 |          | Upstate cities,<br>June-December,<br>1916 |          | Rural New York,<br>June-December,<br>1916 |          |
|                                                  | Number                                 | Per cent | Number                                    | Per cent | Number                                    | Per cent |
| Total.....                                       | 7,496                                  | 100.0    | 1,300                                     | 100.0    | 2,886                                     | 100.0    |
| Under 5 years.....                               | 5,902                                  | 78.7     | 840                                       | 64.6     | 1,575                                     | 54.6     |
| Under 10 years.....                              | 7,157                                  | 95.5     | 1,114                                     | 85.7     | 2,365                                     | 82.0     |
| Under 15 years (New York City,<br>under 16)..... | 7,367                                  | 98.3     | 1,204                                     | 92.6     | 2,596                                     | 90.0     |
| Over 15 years (New York City,<br>over 16).....   | 129                                    | 1.7      | 96                                        | 7.4      | 290                                       | 10.0     |
|                                                  | DEATHS                                 |          |                                           |          |                                           |          |
|                                                  | January-<br>December, 1916             |          | June-December,<br>1916                    |          | June-December,<br>1916                    |          |
|                                                  | Number                                 | Per cent | Number                                    | Per cent | Number                                    | Per cent |
| Total.....                                       | 2,448                                  | 100.0    | 294                                       | 100.0    | 572                                       | 100.0    |
| Under 5 years.....                               | 1,928                                  | 78.8     | 174                                       | 59.2     | 260                                       | 45.5     |
| Under 10 years.....                              | 2,315                                  | 94.6     | 242                                       | 82.3     | 406                                       | 71.1     |
| Under 15 years.....                              | 2,375                                  | 97.0     | 264                                       | 89.8     | 462                                       | 80.9     |
| Over 15 years.....                               | 73                                     | 3.0      | 30                                        | 10.2     | 109                                       | 19.1     |

\* Nicoll, New York State J. Med., 17: 270, 1917.



Specific Morbidity Rates Adjusted to Both Age Group and Density of Population. Godfrey (G 10) analyzed the case, death and fatality

CHART XIII  
POLIOMYELITIS  
DISTRIBUTION BY POPULATION DENSITY  
NEW YORK STATE, 1916

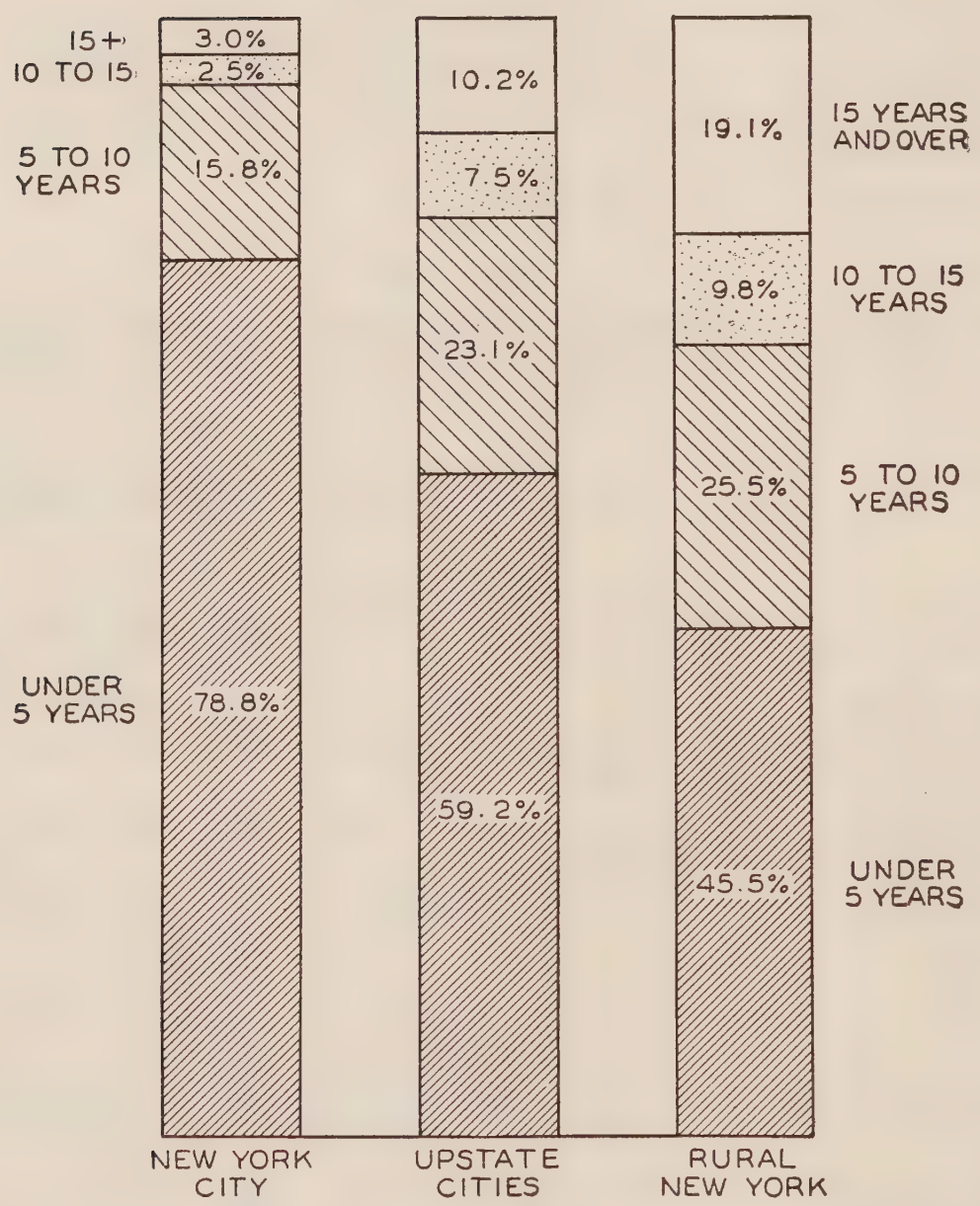


CHART XIII. From Nicoll, Am. J. Dis. Child. 14: 69, 1917

rates according to size of community of 18,299 cases and 4337 deaths from poliomyelitis occurring in New York State, 1915-1924. These are shown in Chart V.

In Table 50 he has shown, by 5 year age groups, the specific case and death rates per 100,000 population for the various population groups, for the years 1920-1924. "The comparatively high case and death rates in places over 10,000 as contrasted with smaller places, of ages under 5 is in contrast with the crude case and death rates. The comparatively low case and death rates at all ages in places of 2,500 to 10,000 and the high case and death rates, especially the former, in places under 2,500 are perhaps worthy of remark."

**Age Distribution as Related to Latitude.** A geographic factor of latitude or climate has been shown by Doull (1928, D 16) to affect the age distribution of deaths from certain of the contagious diseases of childhood. Thus in diphtheria, scarlet fever, and poliomyelitis, there

TABLE 50

AVERAGE RATES PER 100,000 POPULATION AT EACH AGE, 1920-1924 (BASED ON 1922 POPULATION ESTIMATES)\*

| POPULATION GROUP | UNDER 5 YEARS |        | 5 TO 9 YEARS |        | 10 TO 14 YEARS |        | 15 TO 19 YEARS |        | 20 YEARS AND OVER |        |
|------------------|---------------|--------|--------------|--------|----------------|--------|----------------|--------|-------------------|--------|
|                  | Cases         | Deaths | Cases        | Deaths | Cases          | Deaths | Cases          | Deaths | Cases             | Deaths |
| 50,000-200,000   | 63            | 5.2    | 27           | 3.0    | 12             | 3.5    | 7              | 2.8    | 1.0               | 0.3    |
| 20,000-50,000    | 54            | 9.2    | 22           | 2.1    | 10             | 2.7    | 8              | 1.9    | 1.3               | 0.3    |
| 10,000-20,000    | 44            | 7.4    | 26           | 4.3    | 18             | 2.9    | 14             | 1.2    | 1.5               | 0.6    |
| 5,000-10,000     | 32            | 4.8    | 14           | 4.0    | 10             | 2.2    | 5              | 0      | 0.6               | 0      |
| 2,500-5,000      | 46            | 6.7    | 25           | 2.3    | 15             | 3.1    | 10             | 0.9    | 0.9               | 0.1    |
| All others       | 43            | 6.8    | 32           | 4.4    | 23             | 3.8    | 16             | 1.7    | 2.1               | 0.7    |

\* Godfrey, Am. J. Pub. Health, 18: 631, 1928.

is a higher concentration of deaths in early childhood in tropical and sub-tropical than in colder climates. This is not true of measles and whooping cough.

Table 51, compiled by Doull from the mortality statistics of the United States Registration Area, shows a comparison between these diseases. In Chart XIV which we have drawn from his figures, the difference is seen very plainly.

Since morbidity figures for these diseases are not available by age, Doull was not certain whether the high concentration of deaths from diphtheria, scarlet fever, and poliomyelitis in the younger ages in the South is due to a corresponding concentration of cases or to a relatively high case fatality. He believed, from the scant data at his command, that so far as diphtheria and scarlet fever were concerned a concentra-



CHART XIV

# POLIOMYELITIS AND OTHER DISEASES

PER CENT OF DEATHS UNDER THREE YEARS  
IN NORTHERN AND SOUTHERN STATES

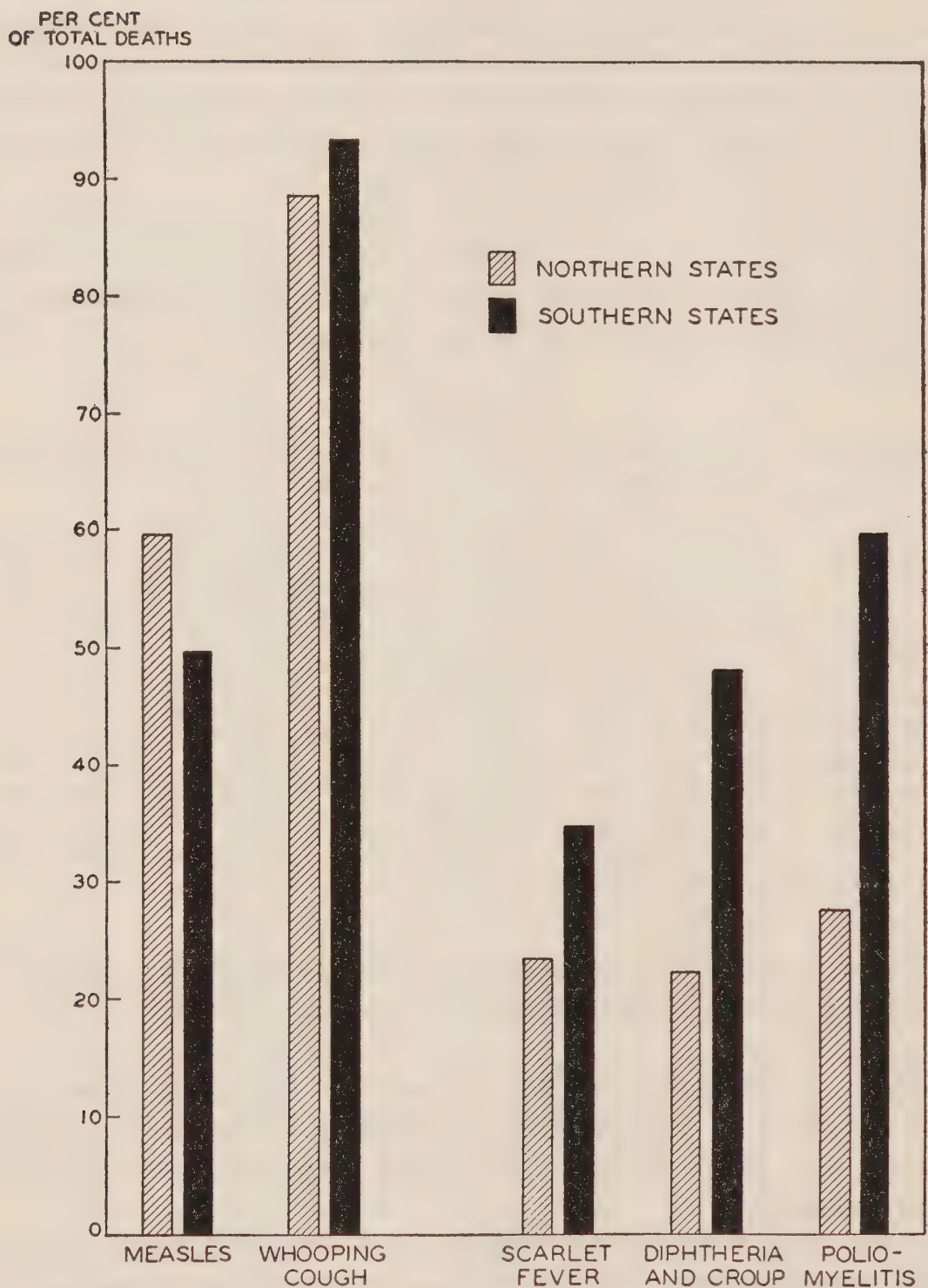


CHART XIV. Proportion of total deaths from measles, whooping cough, diphtheria, scarlet fever, and poliomyelitis, occurring in the age group 0-2 years in northern "rural" and in southern states of the United States Registration Area. (Figures from Doull, Am. J. Hyg. 8: 633, 1928.) For figures from which this chart has been made and for list of states classified as northern and southern see Table 51.

tion of cases in the younger age groups was at least partly responsible, though an increased case fatality in these ages might also be a contributory factor.

It is noted especially that in measles and whooping cough, diseases to which susceptibility is almost universal, the difference in age incidence in North and South is not very great. In diphtheria and scarlet fever, to which susceptibility is lower, the difference is marked. In poliomyelitis, to which susceptibility is lowest, the difference is greatest.

TABLE 51

PROPORTION OF TOTAL DEATHS FROM MEASLES, WHOOPING COUGH, SCARLET FEVER, DIPHTHERIA AND ANTERIOR POLIOMYELITIS, OCCURRING IN THE AGE GROUP 0-2 YEARS, IN 13 NORTHERN\* "RURAL" AND 8 SOUTHERN† STATES OF THE UNITED STATES REGISTRATION AREA‡

| DISEASE             | TOTAL NUMBER OF DEATHS 1917-1924 |                 | DEATHS UNDER 3 YEARS (PER CENT OF TOTAL) |                 |
|---------------------|----------------------------------|-----------------|------------------------------------------|-----------------|
|                     | Northern states                  | Southern states | Northern states                          | Southern states |
| Measles.....        | 8,107                            | 9,657           | 59.64                                    | 49.88           |
| Whooping cough..... | 10,132                           | 8,821           | 88.51                                    | 93.21           |
| Scarlet fever.....  | 6,416                            | 1,268           | 23.30                                    | 34.78           |
| Diphtheria.....     | 14,691                           | 10,566          | 22.20                                    | 48.10           |
| Poliomyelitis.....  | 1,601                            | 762             | 27.67                                    | 59.71           |

\* Southern states were: Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, South Carolina, Tennessee, Virginia.

† Northern states were: California, Colorado, Connecticut, Delaware, Illinois, Indiana, Kansas, Maine, Massachusetts, Michigan, Minnesota, Missouri, Montana, Nebraska, New Hampshire, New Jersey, New York, Ohio, Oregon, Pennsylvania, Rhode Island, Utah, Vermont, Washington, Wisconsin, Wyoming.

‡ Doull, *Am. J. Hyg.* 8: 633-648, 1928.

Although the official morbidity reports in the United States are not made by age groups, individual reports of a few epidemics give the age incidence: Francis (F 59) reported the age distribution of 129 of the 143 cases occurring in Texarkana and vicinity in 1913. Eighty-three per cent were in the 0-4 age group. When it is recalled that in the 1916 epidemic in New York City, only 78 per cent of the cases were in the 0-4 age group, it will be realized that latitude may be a more important factor than density of population in determining the age distribution.

In the Fort Worth, Texas, outbreak in 1928, reported by Davis



(D 7), 67 per cent were in the 0–5 age group.  Acqua (A 8) reports that of the 73 cases observed in the Pediatric Clinic of Parma, 1916–1925, 76.7 per cent were under 5 years, 98.6 per cent were under 10 years.

In contrast to these, the age distribution of the cases in the Manitoba epidemic of 1928 (M 31) might be cited: 30.5 per cent were under 5; 35.4 per cent were 5–9; 18.1 per cent were 10–14; 16 per cent were 15 or over.

**Age Trends.** In the earliest outbreaks of poliomyelitis, the disease was reported to be limited to the younger age groups.  Thus Colmer (C 22) in the first account of an outbreak in the United States, occurring in Louisiana in 1841, said that of the 8 or 10 cases of which he had heard, all were under 2 years of age.  Bull’s (B 39) account of the 1868 epidemic in Sweden states that 12 of the 14 cases were between 4 and 10 years of age.  Medin’s epoch-making report (M 32) of the 44 cases occurring in Stockholm in 1887 gives the ages of these cases as:

|                         |    |
|-------------------------|----|
| Under 6 months.....     | 5  |
| 6 months to 1 year..... | 9  |
| 1 to 2 years.....       | 10 |
| 2 to 3 years.....       | 11 |
| 3 to 4 years.....       | 6  |
| 4 to 5 years.....       | 2  |
| 5 to 6 years.....       | 1  |

The fact that in these earliest reports of outbreaks of poliomyelitis the cases were infants and small children, suggests that the idea had become crystallized that “infantile paralysis” was exclusively a disease of these years, “teething paralysis,” and that cases in older children and adults were differently diagnosed, rather than that they did not occur.  On the other hand, Caverly (C 6) as early as 1894, reported the ages of 120 of the 132 cases occurring in the Otter Creek Valley, Vermont, outbreak of 1894:

90 (75 per cent) were under 6 years  
15 (12.5 per cent) were 6 to 14  
15 (12.5 per cent) were over 14

This is in contrast to epidemic encephalitis, with an age incidence which, as Halliday (H 4) points out, “suggests the behavior of a virus attacking what was relatively virgin soil.”  He shows that in Glasgow in 1924, when the first extensive outbreak of epidemic encephalitis occurred, only 15 per cent of the cases were under 10 years; sporadic cases have occurred since, and he predicts that if they continue appear-

ing, further outbreaks will affect mainly the earlier age groups. MacNalty (M 10) has also called attention to the fact that the attack rate of encephalitis has been directly proportional to the density of the population, rather than inversely proportional, as is that of poliomyelitis.

Park and Neal (P 2) give a table of the age incidence of the triad of infectious diseases of the central nervous system during 1926 in New York City.

TABLE 52  
AGE INCIDENCE OF INFECTIOUS DISEASES OF CENTRAL NERVOUS SYSTEM, NEW YORK CITY 1926\*

| AGE                 | CEREBROSPINAL<br>MENINGITIS |        | EPIDEMIC<br>ENCEPHALITIS |        | POLIOMYELITIS |        |
|---------------------|-----------------------------|--------|--------------------------|--------|---------------|--------|
|                     | Cases                       | Deaths | Cases                    | Deaths | Cases         | Deaths |
| 0 to 4 years.....   | 88                          | 59     | 47                       | 24     | 59            | 15     |
| 5 to 9 years.....   | 21                          | 15     | 17                       | 8      | 25            | 3      |
| 10 to 14 years..... | 8                           | 3      | 25                       | 11     | 11            | 7      |
| 15 to 19 years..... | 10                          | 8      | 24                       | 14     | 6             | 3      |
| 20 to 24 years..... | 12                          | 5      | 30                       | 14     | 3             | 1      |
| 25 to 29 years..... | 5                           | 4      | 27                       | 22     | 2             | 1      |
| 30 to 34 years..... | 5                           | 3      | 22                       | 10     | 1             | 0      |
| 35 to 39 years..... | 8                           | 5      | 20                       | 14     | 0             | 0      |
| 40 to 44 years..... | 3                           | 3      | 19                       | 12     | 1             | 1      |
| 45 to 49 years..... | 2                           | 2      | 16                       | 13     | 1             | 1      |
| 50 to 54 years..... | 3                           | 3      | 17                       | 13     | 0             | 0      |
|                     | 165                         | 108    | 264                      | 155    | 109           | 32     |

\* Park and Neal, Southwestern Med. 11: 523, 1927.

**Recent Age Trends.** It has recently been noted that a larger and larger percentage of cases of poliomyelitis is occurring in the higher age groups.

Forsbeck and Luther (1930, F 57) called attention to such a trend in age distribution in Massachusetts. Up to about 1918, there was little or no change in the age distribution. Since then, the relative number of cases in the 0-4 year group has markedly decreased, and there has been a compensatory increase in the relative number of cases in the age groups 5-9 and 10-14. The percentage of cases occurring in the age group 15-19 and in adult life has remained fairly constant. Table 53, taken from a table prepared by these authors, and supplemented by figures for 1930 and 1931 obtained through the courtesy of Dr. Gaylord W. Anderson, shows this trend.



Knowlton (K 19) called attention to the increased percentage of cases over 5 occurring in 1931, an epidemic year, as compared with the distribution for the period 1921–1930. When to these figures are added those for 1916, also an epidemic year, the trend is very marked.

TABLE 53  
PERCENTAGE DISTRIBUTION OF ANTERIOR POLIOMYELITIS IN MASSACHUSETTS, BY  
AGE GROUPS, 1912–1931\*

| YEAR  | CASES | 0 TO 4 YEARS    | 5 TO 9 YEARS    | 10 TO 19 YEARS    |                   | 20+ YEARS       |
|-------|-------|-----------------|-----------------|-------------------|-------------------|-----------------|
|       |       | <i>per cent</i> | <i>per cent</i> | <i>per cent</i>   |                   | <i>per cent</i> |
| 1912  | 169   | 66.7            | 16.7            | 8.9               |                   | 7.7             |
| 1913  | 361   | 62.0            | 19.9            | 15.1              |                   | 3.0             |
| 1914  | 151   | 64.6            | 15.6            | 10.4              |                   | 9.4             |
| 1915  | 135   | 62.3            | 19.7            | 13.9              |                   | 4.1             |
| 1916  | 1,927 | 69.7            | 19.8            | 5.9               |                   | 4.6             |
| 1917† |       |                 |                 |                   |                   |                 |
|       |       |                 |                 | 10 TO 14<br>YEARS | 15 TO 19<br>YEARS |                 |
|       |       |                 |                 | <i>per cent</i>   | <i>per cent</i>   |                 |
| 1918  | 99    | 66.3            | 13.7            | 7.4               | 5.2               | 7.4             |
| 1919  | 66    | 61.9            | 20.6            | 9.5               | 4.8               | 3.2             |
| 1920  | 696   | 53.2            | 25.3            | 10.3              | 5.2               | 6.0             |
| 1921  | 233   | 43.6            | 23.5            | 13.3              | 5.8               | 13.8            |
| 1922  | 217   | 49.8            | 25.1            | 13.0              | 7.3               | 4.8             |
| 1923  | 223   | 59.4            | 21.7            | 9.4               | 3.8               | 5.7             |
| 1924  | 277   | 47.0            | 24.2            | 14.6              | 5.6               | 8.6             |
| 1925  | 167   | 50.3            | 16.8            | 17.4              | 5.0               | 10.5            |
| 1926  | 245   | 44.8            | 29.3            | 9.6               | 6.3               | 10.0            |
| 1927  | 1,189 | 45.9            | 30.9            | 11.4              | 6.0               | 5.8             |
| 1928  | 434   | 36.9            | 31.6            | 16.1              | 6.9               | 8.5             |
| 1929  | 119   | 27.8            | 33.1            | 16.5              | 13.0              | 9.6             |
| 1930  | 503   | 38.1            | 38.9            | 12.6              | 5.2               | 5.2             |
| 1931  | 1,428 | 27.6            | 40.6            | 16.2              | 8.0               | 7.6             |

\* Forsbeck and Luther, New England J. Med. 203: 1115, 1930. Figures for 1930 and 1931 are available through the courtesy of Dr. Gaylord W. Anderson of the Massachusetts State Board of Health.

† Missing.

The most striking example of this trend is seen, however, in the age incidence in the three major epidemics from which New York City has suffered. Table 55 gives the age grouping for New York City, 1907, 1916 and 1931. The figures for 1907 are, unfortunately, not given by standard age groups, so that, to facilitate comparison, the cases for the 1916 epidemic have been given by both age groupings.

It is interesting to compare this 1931 age distribution in New York City with that reported by Nicoll (N 28) in Table 49 for rural New York in 1916. We have shown this in Table 56.

Limper, Thelander and Shaw (L 60) have called attention to the age incidence in the California epidemic of 1930. Of 1835 cases reported in California in 1930, 21.5 per cent were in persons 15 years of age and over; the adult incidence of 19.4 per cent in rural sections was exceeded by the adult incidence of 23.6 per cent in the larger cities, chiefly Los Angeles and San Francisco. They comment that "this is particularly surprising in view of the fact that much the same areas of the state involved in the present epidemic were affected by the disease in 1925

TABLE 54

CASES OF POLIOMYELITIS IN CONNECTICUT BY AGE GROUPS, 1916, 1921-1930, 1931\*

|           |                 | UNDER 5 YEARS | 5 TO 9 YEARS | 10 TO 14 YEARS | 15 TO 19 YEARS | 20 TO 29 YEARS | 30+ YEARS | TOTAL | AGE NOT GIVEN | TOTAL |
|-----------|-----------------|---------------|--------------|----------------|----------------|----------------|-----------|-------|---------------|-------|
| 1916      | { Cases.....    | 497           | 179          | 64             | 27             | 12             | 22        | 801   | 55            | 856   |
|           | { Per cent..... | 62.0          | 22.3         | 8.0            | 3.3            | 1.3            | 2.7       | 100   | —             | —     |
| 1921-1930 | { Cases.....    | 345           | 186          | 88             | 37             | 38             | 25        | 719   | 50            | 769   |
|           | { Per cent..... | 48.0          | 25.9         | 12.2           | 5.1            | 5.3            | 3.5       | 100   | —             | —     |
| 1931      | { Cases.....    | 389           | 425          | 175            | 68             | 35             | 22        | 1,114 | 19            | 1,133 |
|           | { Per cent..... | 34.9          | 38.1         | 15.7           | 6.1            | 3.2            | 2.0       | 100   | —             | —     |

\* Age distribution for 1916 is taken from Lavinder, Freeman and Frost, Public Health Bulletin, 91: 269. Age distribution for 1921-1930 and 1931 is taken from Knowlton, Connecticut Health Bull. 46: 3-13, 1932.

and 1927, the recent epidemic being characterized by a higher adult percentage in the state as a whole than that of 18.3 per cent in 1927, and the recent percentage (23.6 per cent) of adult urban cases being higher than the 16.7 per cent of adult urban cases in 1927."

Zollikofer and Custer (Z 9) report that in the 1931 epidemic which occurred in the St. Gallen Rhine Valley and environs, they were struck by the number of youths and adults affected: exactly half of the 70 cases which they saw were 13 years of age or over.

*Mortality.* This trend is seen in the mortality as well as the morbidity figures. Table 58 has been compiled by Das of Johns Hopkins University from the Mortality Statistics of the United States



Census for the years 1910–1928 (permission to use this table has been given to us by Dr. Frost). It shows, without exception, for the states studied, a lower percentage under 5 years for the 1924–1928 period than for the preceding periods.

No figures are available which give the specific attack rates by age groups over a period of years. We know that there has been a marked

TABLE 55  
CASES, NEW YORK CITY, 1907, 1916 AND 1931; PERCENTAGE DISTRIBUTION BY AGE GROUPS\*

| AGE GROUP           | 1907<br>728<br>CASES | 1916<br>9,131<br>CASES | AGE GROUP           | 1916<br>9,131<br>CASES | 1931<br>3,918<br>CASES |
|---------------------|----------------------|------------------------|---------------------|------------------------|------------------------|
|                     | <i>per cent</i>      | <i>per cent</i>        |                     | <i>per cent</i>        | <i>per cent</i>        |
| Under 1 year.....   | 8.5                  | 11.1                   | Under 1 year.....   | 11.1                   | 4.2                    |
| 1 to 5 years.....   | 82.0                 | 74.7                   | 0 to 4 years.....   | 79.2                   | 53.3                   |
| 6 to 10 years.....  | 6.4                  | 10.5                   | 5 to 9 years.....   | 16.2                   | 30.7                   |
| 11 to 15 years..... | 1.9                  | 1.9                    | 10 to 14 years..... | 2.4                    | 10.2                   |
| 16 to 20 years..... | 0.7                  | 0.6                    | 15 to 19 years..... | 0.8                    | 2.9                    |
| Adults.....         | 0.4                  | 1.2                    | 20+ years.....      | 1.3                    | 2.7                    |

\* The age incidence for the 1907 and 1916 epidemics are from Lavinder, Freeman and Frost, Public Health Bull. 91, 1918. The age incidence for the 1931 epidemic has been given us through the courtesy of the New York City Health Department.

TABLE 56  
AGE INCIDENCE, RURAL NEW YORK, 1916,\* AND NEW YORK CITY, 1931†

| AGE GROUP           | RURAL NEW YORK,<br>JUNE–DECEMBER,<br>1916 | NEW YORK CITY,<br>1931 |
|---------------------|-------------------------------------------|------------------------|
| Under 5 years.....  | 54.6                                      | 53.3                   |
| Under 10 years..... | 82.0                                      | 84.0                   |
| Under 15 years..... | 90.0                                      | 94.2                   |
| Over 15 years.....  | 10.0                                      | 5.6                    |

\* Nicoll, New York State J. Med. 17: 270, 1917.  
† Unpublished figures by courtesy of New York City Department of Health.

change in the population makeup of the United States as regards age even in the last ten years. In 1930, the 0–4 group in the United States was only 9.3 per cent of the total population, whereas in 1920 it was 10.9 per cent, and in 1910, 11.6 per cent. (We have taken these figures from the *World's Almanac* for 1932.) Whether the rates adjusted to the age distribution of the population will show so marked a trend as

the percentage distribution remains to be seen, since the figures are not yet available.

TABLE 57  
PERCENTAGE OF POLIOMYELITIS CASES OCCURRING AMONG ADULTS IN CALIFORNIA,  
1927 AND 1930\*

|            | 1927 | 1930 |
|------------|------|------|
| Urban..... | 16.7 | 23.6 |
| Rural..... | 19.9 | 19.4 |

\* Limper, Thelander and Shaw, J. Prev. Med. 5: 475, 1931.

TABLE 58  
PERCENTAGE OF TOTAL DEATHS OCCURRING UNDER 5 YEARS FROM POLIOMYELITIS  
IN EACH OF THE REGISTRATION STATES OF 1910, IN SUCCESSIVE  
5-YEAR PERIODS, 1910-1928\*

| STATE              | PERIODS   |           |           |           |
|--------------------|-----------|-----------|-----------|-----------|
|                    | 1910-1914 | 1915-1918 | 1919-1923 | 1924-1928 |
| Maryland.....      | 74        | 73        | 65        | 57        |
| Ohio.....          | 72        | 61        | 54        | 40        |
| Utah.....          | 71        | 44        | 71        | 36        |
| Montana.....       | 69        | 43        | 52        | 23        |
| New Jersey.....    | 65        | 72        | 49        | 43        |
| Pennsylvania.....  | 65        | 68        | 50        | 49        |
| Rhode Island.....  | 65        | 71        | 45        | 32        |
| Indiana.....       | 64        | 68        | 59        | 43        |
| New York.....      | 62        | 70        | 44        | 35        |
| Massachusetts..... | 58        | 65        | 42        | 37        |
| California.....    | 57        | 56        | 38        | 34        |
| Connecticut.....   | 57        | 55        | 55        | 36        |
| Michigan.....      | 57        | 51        | 42        | 36        |
| Wisconsin.....     | 55        | 49        | 37        | 32        |
| New Hampshire..... | 54        | 59        | 26        | 18        |
| Washington.....    | 49        | 28        | 22        | 15        |
| Colorado.....      | 48        | 59        | 63        | 41        |
| Minnesota.....     | 46        | 32        | 34        | 18        |
| Maine.....         | 43        | 35        | 41        | 30        |
| Vermont.....       | 36        | 30        | 30        | 14        |

\* Das, Unpublished report, Johns Hopkins University. Permission to reproduce this table has been given to us by Dr. W. H. Frost.

The explanation of this trend is not known. Anderson of the Massachusetts State Board of Health (personal communication) has pointed



out a similar trend in the age incidence of diphtheria in Massachusetts. His figures are given in Table 59. This was marked until the extensive immunization of children of school age caused a temporary rise in the percentage of preschool ages, but has, in spite of this factor, recently again become visible. The age incidence for measles in Massachusetts does not, however, show this change.

Aycock (personal communication) suggested to us that better diagnosis, a more general appreciation of the fact that poliomyelitis is not exclusively a disease of infants and young children is a factor in the trend. While no one can doubt that better diagnosis must be reckoned

TABLE 59  
DIPHTHERIA DEATHS, COMMONWEALTH OF MASSACHUSETTS, 1880-1930, BY AGE GROUPS\*

| PERIOD    | 0 TO 4 YEARS |             | 5 TO 9 YEARS |             | 10 TO 14 YEARS |             | 15+ YEARS   |             | TOTAL | AGE UN-<br>KNOWN |
|-----------|--------------|-------------|--------------|-------------|----------------|-------------|-------------|-------------|-------|------------------|
|           | Num-<br>ber  | Per<br>cent | Num-<br>ber  | Per<br>cent | Num-<br>ber    | Per<br>cent | Num-<br>ber | Per<br>cent |       |                  |
| 1880-1885 | 5,835        | 65.3        | 2,228        | 24.9        | 462            | 5.2         | 402         | 4.5         | 8,944 | 17               |
| 1886-1890 | 5,621        | 63.2        | 2,305        | 26.0        | 497            | 5.6         | 424         | 4.8         | 8,857 | —                |
| 1891-1895 | 4,912        | 64.2        | 2,035        | 26.7        | 353            | 4.6         | 345         | 4.5         | 7,652 | —                |
| 1896-1900 | 4,161        | 65.4        | 1,554        | 24.6        | 299            | 4.7         | 317         | 5.0         | 6,331 | —                |
| 1901-1905 | 2,778        | 65.2        | 1,052        | 24.6        | 223            | 5.2         | 206         | 4.8         | 4,259 | —                |
| 1906-1910 | 2,228        | 61.7        | 986          | 27.2        | 196            | 5.4         | 205         | 5.7         | 3,615 | —                |
| 1911-1915 | 1,846        | 60.8        | 852          | 28.1        | 182            | 6.0         | 156         | 5.1         | 3,036 | —                |
| 1916-1920 | 1,867        | 57.3        | 1,012        | 31.1        | 191            | 5.9         | 189         | 5.8         | 3,259 | —                |
| 1921-1925 | 1,570        | 59.1        | 827          | 31.1        | 135            | 5.1         | 127         | 4.8         | 2,659 | —                |
| 1926-1930 | 641          | 53.3        | 408          | 33.9        | 60             | 5.0         | 95          | 7.9         | 1,204 | —                |

\* Anderson, Massachusetts State Board of Health (personal communication).

with in this connection, the differences seem to be too great to be explained chiefly on such a basis. Nor would the mortality figures compiled by Das nor the diphtheria of Anderson lend weight to this as the sole explanation.

Jungeblut and Engle (personal communication) see in the trend of age incidence in the United States a result of the drastic restriction of immigration in 1915. They argue that, since resistance to poliomyelitis is primarily a function of maturation, the age incidence in a heterogeneous population such as New York City will vary with the percentage of persons of Northern and Southern nationalities. The greater the percentage of slowly maturing North-Europeans, the higher will

be the age incidence; the greater the percentage of quickly maturing South-Europeans, the lower the age incidence. Since it has been the South-Europeans who were especially excluded by the quota law, the population makeup is gradually shifting toward a higher proportion of North-Europeans and their children. We have no data bearing upon this theory. The attack rates for the various races in the 1931 New York City epidemic are not yet available.

**Variations in Age Distribution during the Course of Epidemics.** A change in the age distribution of the cases has been noted during the course of various outbreaks of poliomyelitis, the younger ages showing a relatively greater proportion early in the epidemic, the older age groups later. No explanation for this variation has been given.

Shidler (S 40) states that in the Nebraska outbreak of 1909:

- 1. Of the first 60 cases, 75 per cent were under 10 years,
- 2. Of the last 19 cases, 48 per cent were under 10 years.

Lavinder, Freeman and Frost (L 16) in their study of the New York City epidemic of 1916 likewise noted this tendency. They divided their cases into successive groups of approximately 500 cases each, in the order of their onset. The age distribution of the successive groups was tabulated for Manhattan and Brooklyn only, since the numbers in the other boroughs were not sufficiently large. They report the percentage of cases 6 years of age and over in the successive groups.

BROOKLYN, PERCENTAGE OF CASES 6 YEARS OF AGE AND OVER

| Period |        |            |         | Per Cent |
|--------|--------|------------|---------|----------|
| 1      | May    | 5-June     | 27..... | 6.0      |
| 2      | June   | 27-July    | 5.....  | 10.0     |
| 3      | July   | 6-July     | 12..... | 12.9     |
| 4      | July   | 13-July    | 19..... | 13.7     |
| 5      | July   | 20-July    | 25..... | 13.0     |
| 6      | July   | 26-July    | 31..... | 10.7     |
| 7      | August | 1-August   | 6.....  | 12.5     |
| 8      | August | 7-August   | 18..... | 16.1     |
| 9      | August | 19-October | 30..... | 20.2     |

MANHATTAN, PERCENTAGE OF CASES 6 YEARS AND OVER

| Period |        |            |         | Per Cent |
|--------|--------|------------|---------|----------|
| 1      | May    | 6-July     | 22..... | 8.8      |
| 2      | July   | 23-August  | 2.....  | 12.3     |
| 3      | August | 3-August   | 13..... | 15.1     |
| 4      | August | 14-August  | 26..... | 17.2     |
| 5      | August | 27-October | 30..... | 15.6     |



They comment that “as is very clearly shown by the above tables, the percentages of cases in persons 6 years and over showed a very marked tendency to increase with the progress of the epidemic. It is of interest to note that in Brooklyn the periods of decrease in percentage of cases 6 years and over (periods 5 and 6) correspond quite accurately to the time when the epidemic, after reaching its apparent crest, again took an upward turn, the number of cases increasing rapidly until the true crest was reached. It would appear, therefore, that there was in the epidemic a stage marked by a very low percentage of cases in persons 6 years and over, which may be termed the stage of invasion, and that the percentage of cases in the age groups 6 years

TABLE 60  
AGE AND SEX DISTRIBUTION OF POLIOMYELITIS BY 3-MONTH PERIODS IN THE 1927 OHIO EPIDEMIC\*

|              | AGE  | JULY-SEPTEMBER CASES |          | OCTOBER-DECEMBER CASES |          | TOTAL CASES |          |
|--------------|------|----------------------|----------|------------------------|----------|-------------|----------|
|              |      | Num-ber              | Per-cent | Num-ber                | Per-cent | Num-ber     | Per-cent |
| Males.....   | 0-5  | 301                  | 55.7     | 98                     | 47.8     | 399         | 53.6     |
|              | 6-20 | 212                  | 39.3     | 101                    | 49.2     | 313         | 42.0     |
|              | 21+  | 27                   | 5.0      | 6                      | 3.0      | 33          | 4.4      |
| Females..... | 0-5  | 198                  | 53.1     | 57                     | 34.8     | 255         | 47.4     |
|              | 6-20 | 160                  | 42.9     | 98                     | 59.8     | 258         | 48.0     |
|              | 21+  | 15                   | 4.0      | 9                      | 5.4      | 24          | 4.6      |

\* Oldt, Poliomyelitis in Ohio in 1927.

and over increased gradually, except where the progress of the epidemic was temporarily halted. The state of invasion again appeared, the percentage in the higher ages again increasing with the progress of the new rise.” Corresponding mortality or fatality figures are not given.

Oldt (O 1) reports that in the 1927 outbreak of poliomyelitis in Ohio, in the July-September group, there was a higher percentage of cases in the preschool group, while in the October-December group there was a higher proportion in the 6-20 group. When he further subdivided his cases according to sex, he found that the age distribution for the two periods differed markedly in the two sexes, the percentage in the upper age groups during the second period being higher in the females than in the males.

**Poliomyelitis in the First Year of Life.** The incidence of poliomyelitis in children under one year is lower than in those in the years immediately succeeding. This fact has been taken to represent a passive immunity in infants, derived from the mother, an inference which is borne out by the demonstration of Aycock and Kramer (A 45) that the neutralizing power of the serum from the cord blood of 11 out of 12 new-born infants corresponded to that of their mothers. Shaughnessy, Harmon and Gordon (S 33) tested 5 normal infants, finding that 2, aged 7 weeks and 6 months, neutralized, while 3, aged 9, 12 and 20 months, did not neutralize.

If the protection of young infants is due to an inherited immunity, the level of immunity in the new-born should approximate that of the adult females of their particular locality and sphere of life, varying, that is, with the same factors that influence immunity in the adult.

We know, however, that, in spite of the inherited antibodies, infants do not enjoy a degree of protection equal to that of adults. Thus, while the rate of attack is lower in infants under 6 months than in other young children, it is markedly higher than that of the adult groups, though the exposure must be much less. Thus, in 1916, the rate for infants under 1 year was 867 per 100,000 while for persons 25 or over, the rate was under 1 per 100,000 (Lavinder, Freeman and Frost, L 16). We have not been able to find in the literature specific attack rates by months for infants under 1 year.

Under *Case Fatality*, we have called attention to the high case fatality in infants under 1 year. We cited Weisenburg's figures for Philadelphia, 1916 (W 12), which suggest that in infants maternally nursed, the disease may not be so fatal as in those otherwise fed.

Tables 61, 62, and 63 show the distribution of cases through the months of the first year of life. In none of the three instances quoted is reference made to whether or not the infants were maternally nursed.

How long this inherited protection lasts, we do not know. By analogy with diphtheria, the duration has been assumed to be about 6 months. The above figures for the 1916 epidemic in New York City, and for the Ohio epidemic of 1927, show that the ratio of cases in the second 6 months to those in the first 6 months was about 3:1. This does not, however, necessarily imply that babies in the second 6 months are three times as susceptible to poliomyelitis, since those under 6 months are relatively much less exposed to infection than those over 6 months.

Oldt compared the incidence of poliomyelitis and diphtheria in the



first year of life, in Ohio. He pointed out that the ratio of cases under 6 months to cases of all ages is a little less than twice as great for poliomyelitis as for diphtheria, but more than three times as great for polio-

TABLE 61  
INCIDENCE BY MONTHS IN THE CASES UNDER 2 YEARS OF AGE OCCURRING IN WASHINGTON STATE IN 1910\*

|                                         | AGE IN MONTHS |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |     |
|-----------------------------------------|---------------|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|-----|
|                                         | 1             | 2 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 20 | 21  |
| Cases.....                              | 1             | 1 | 1 | 1 | 2 | 5 | 2  | 5  | 6  | 2  | 2  | 6  | 6  | 4  | 11 | 4  | 2   |
| Total under 1 year.....                 |               |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    | 18  |
| Total under 2 years.....                |               |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    | 61  |
| Total cases, all ages, in outbreak..... |               |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    | 331 |

\* Kelley, Gellhorn and Manning, Infantile Paralysis in Washington, 1910.

TABLE 62  
DISTRIBUTION OF CASES AND DEATHS UNDER 1 YEAR IN NEW YORK CITY, 1916\*

|             | AGE IN MONTHS   |    |    |    |    |    |    |     |     |     |     |     | TOTAL |
|-------------|-----------------|----|----|----|----|----|----|-----|-----|-----|-----|-----|-------|
|             | Un-<br>der<br>1 | 1  | 2  | 3  | 4  | 5  | 6  | 7   | 8   | 9   | 10  | 11  |       |
| Cases.....  | 7               | 19 | 27 | 52 | 70 | 64 | 98 | 118 | 104 | 153 | 149 | 121 | 982   |
| Deaths..... | 3               | 13 | 10 | 17 | 24 | 34 | 45 | 45  | 44  | 52  | 73  | 63  | 423   |

\* New York City Health Dept. Monograph, 1916, p. 376.

TABLE 63  
COMPARISON BETWEEN POLIOMYELITIS AND DIPHTHERIA IN CHILDREN UNDER 1 YEAR IN OHIO, 1927\*

|                    | AGE IN MONTHS   |   |   |   |   |   |   |   |   |   |    |    | TOTAL | TOTAL<br>CASES,<br>ALL<br>AGES | PER<br>CENT<br>OF<br>TOTAL |
|--------------------|-----------------|---|---|---|---|---|---|---|---|---|----|----|-------|--------------------------------|----------------------------|
|                    | Un-<br>der<br>1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |       |                                |                            |
| Poliomyelitis..... | 1               | 1 | 3 | 3 | 2 | 0 | 8 | 2 | 6 | 2 | 5  | 5  | 38    | 1,350                          | 2.8                        |
| Diphtheria.....    | 4               | 2 | 2 | 3 | 1 | 2 | 2 | 4 | 2 | 7 | 3  | 3  | 35    | 3,600                          | 0.9                        |

\* Oldt, Poliomyelitis in Ohio in 1927.

myelitis as for diphtheria in the second 6 months. Oldt believes that the explanation of this lies in the exposure incident to the seasonal variation of the two diseases, since infants are more likely to be taken out in the summer and early fall when poliomyelitis is prevalent, than in the later fall and winter when diphtheria is prevalent, a difference more marked in the second than in the first 6 months of life. The series are too small to more than raise the point.

### SEX INCIDENCE

In common with other infectious diseases of the central nervous system, poliomyelitis consistently attacks more males than females. The ratio between the sexes has varied somewhat in different outbreaks, but the excess of males over females is one of the most constant epidemiological features of the disease.

**Morbidity.** The official morbidity reports in the United States are not given by sex. We have, therefore, compiled Table 64 from various reports in which the cases are given by sex.

The ratio of male to female cases in the 36,000 cases summarized in Table 64 is 1.3 to 1.0. It is noticeable that the larger series, those comprising a thousand or more cases, do not depart greatly from this ratio; while in the smaller series where wider chance fluctuation is possible, the difference is apt to be more marked. Forsbeck and Luther (F 57) in the series of more than 7000 cases occurring in Massachusetts from 1908 to 1929, with the exception of 1911 and 1917, note that in the epidemic years, the variation from the mean ratio of the sexes has been very small. Only twice in the 19 years covered have the females outnumbered the males. These two years had fewer cases than any other year reported upon.

**Mortality and Case Fatality.** The United States census reports for the 13 years, 1916 to 1928, of deaths from poliomyelitis, give 11,292 males and 8809 females, or a ratio of 1.28 males to 1 female. If these deaths are subdivided into negro and white, the deaths and ratio are:

|              | <i>Male Deaths</i> | <i>Female Deaths</i> | <i>Ratio: Males to<br/>1 Female</i> |
|--------------|--------------------|----------------------|-------------------------------------|
| White.....   | 10,684             | 8,251                | 1.29 to 1                           |
| Colored..... | 608                | 558                  | 1.09 to 1                           |

When the white deaths alone are considered it will be seen that the mortality ratio for the sexes approximates the morbidity ratio, for the series in Table 64, although the negro deaths do not. Whether the difference in susceptibility in the sexes is really less marked in the



TABLE 64  
DISTRIBUTION OF CASES BY SEX, VARIOUS REPORTS

| AUTHOR                                                          | REFER-<br>ENCE | LOCALITY                                         | YEAR      | MALES  | FE-<br>MALES | RATIO:<br>MALES TO<br>1 FEMALE |
|-----------------------------------------------------------------|----------------|--------------------------------------------------|-----------|--------|--------------|--------------------------------|
| Seeligmüller                                                    | S 26           | Halle, Germany                                   | 1866-1878 | 44     | 31           | 1.41:1                         |
| Caverley                                                        | C 6            | Otter Creek Valley,<br>Vermont                   | 1894      | 39     | 22           | 1.77:1                         |
| Leegaard                                                        | L 25           | Norway                                           | 1905      | 472    | 365          | 1.29:1                         |
| Wickman                                                         | W 21           | Sweden                                           | 1905      | 591    | 426          | 1.38:1                         |
| Forsbeck and Lu-<br>ther                                        | F 57           | Massachusetts                                    | 1908-1929 | 4,048  | 3,106        | 1.30:1                         |
| Hill                                                            | H 22           | Minnesota                                        | 1909      | 193    | 139          | 1.38:1                         |
| Dixon                                                           | D 14           | Pennsylvania                                     | 1910      | 437    | 336          | 1.30:1                         |
| Frost                                                           | F 71           | Cincinnati, Ohio                                 | 1911      | 91     | 59           | 1.54:1                         |
| Wernstedt                                                       | W 14           | Sweden                                           | 1911-1913 | 3,593  | 3,039        | 1.18:1                         |
| Lavinder, Freeman<br>and Frost                                  | L 16           | New York City                                    | 1916      | 5,106  | 3,909        | 1.31:1                         |
| Jemma                                                           | J 4            | Naples, Italy                                    | 1913-1922 | 245    | 184          | 1.33:1                         |
| Acqua                                                           | A 8            | Parma, Italy                                     | 1916-1925 | 33     | 40           | 0.82:1                         |
| Silverman                                                       | S 42           | Syracuse, New<br>York                            | 1922-1929 | 183    | 105          | 1.74:1                         |
| Oldt                                                            | O 1            | Ohio                                             | 1927      | 759    | 555          | 1.36:1                         |
| Medical Research<br>Committee, Uni-<br>versity of Mani-<br>toba | M 31           | Manitoba, Canada                                 | 1928      | 233    | 185          | 1.25:1                         |
| Jenkins                                                         | J 7            | Alberta, Canada                                  | 1927      | 182    | 172          | 1.05:1                         |
| Hardman and<br>McKay                                            | H 11           | Ontario, Canada                                  | 1929      | 267    | 149          | 1.79:1                         |
| McKay and Hard-<br>man                                          | M 5            | Ontario, Canada                                  | 1930      | 371    | 225          | 1.72:1                         |
| Lanpher                                                         | L 14           | Iowa                                             | 1930      | 107    | 71           | 1.50:1                         |
| New York State,<br>Department of<br>Health                      | N 24           | New York State,<br>exclusive of New<br>York City | 1931†     | 1,053  | 736          | 1.43:1                         |
| New York City<br>Health Depart-<br>ment                         | *              | New York City                                    | 1931      | 2,363  | 1,737        | 1.35:1                         |
| Total.....                                                      |                |                                                  |           | 20,410 | 15,591       | 1.30:1                         |

\* Personal communication.

† To December 1.

colored race, or whether the variation is merely incident to the relatively smaller numbers, it is impossible to say

The sex ratio appears, therefore, to be about the same for the cases and for the deaths. It follows that the case fatality is about equal for the sexes.

In individual epidemics, the case fatality for either sex may be higher, though in the larger series the difference is usually not great. In Table 65, the case fatality in four epidemics is shown, in two of which the male fatality is slightly higher, and in two the female.

TABLE 65  
CASE FATALITY BY SEX IN FOUR EPIDEMICS

| AUTHOR                                  | REFER-<br>ENCE | LOCALITY         | YEAR | TOTAL<br>CASES | MALE<br>CASE<br>FATALITY | FEMALE<br>CASE<br>FATALITY |
|-----------------------------------------|----------------|------------------|------|----------------|--------------------------|----------------------------|
| Frost                                   | F 71           | Cincinnati, Ohio | 1911 | 150            | 29.67                    | 32.2                       |
| Frost                                   | F 71           | Iowa             | 1910 | 346            | 17.8                     | 21.3                       |
| Lavinder, Freeman<br>and Frost          | L 16           | New York City    | 1916 | 9,015          | 25.6                     | 23.2                       |
| New York City<br>Health Depart-<br>ment | N 23           | New York City    | 1931 | 4,100          | 12.7                     | 11.6                       |

**Influence of Age on Sex Incidence.** More males than females are affected by poliomyelitis at all ages. Due to the fewer cases in the older age groups, the sex ratio for these tends to be somewhat irregular. The cases reported in Massachusetts, 1908 to 1929 (Forsbeck and Luther, F 57) are typical of the sex and age distribution of cases.

The deaths as recorded by the Mortality Reports, United States Census, for the years 1916 to 1928 indicate that there is a tendency for the proportion of males to increase with age. The ratios at various ages are:

DEATHS, WHITE ONLY, UNITED STATES REGISTRATION AREA, 1916-1928

| Age                 | Male | Female | Ratio |
|---------------------|------|--------|-------|
| Under 5 years.....  | 5766 | 4732   | 1.21  |
| 5 to 9 years.....   | 2162 | 1681   | 1.28  |
| 10 to 14 years..... | 1099 | 859    | 1.27  |
| 15 to 19 years..... | 718  | 434    | 1.65  |
| 20 to 24 years..... | 397  | 233    | 1.70  |
| 25+ years.....      | 542  | 312    | 1.73  |



In Chart XVI, Jungeblut and Engle have shown this increased proportion of male deaths from poliomyelitis with age. They have

CHART XV  
POLIOMYELITIS  
CASES BY AGE AND SEX  
MASSACHUSETTS, 1908-1929

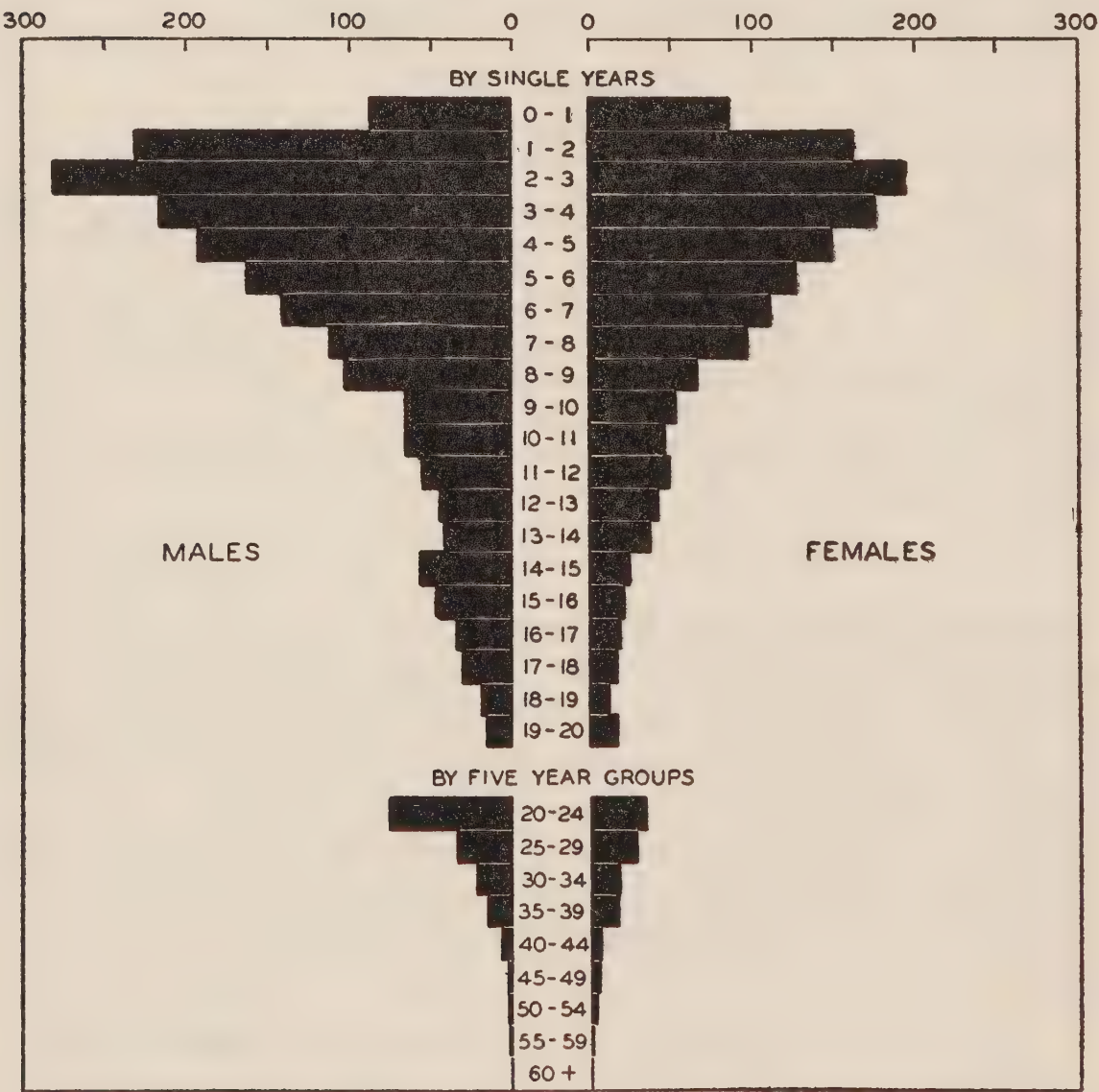


CHART XV. Figures from Forsbeck and Luther, New England J. Med. 203: 1115, 1930.

plotted the number of male deaths to each 1000 deaths from poliomyelitis, the number of male deaths to each 1000 deaths from all causes, and the number of males in each 1000 of the general population in the

ages up to 40 years. The marked predominance of male deaths from poliomyelitis in the years above puberty is clearly shown.

TABLE 66  
CASES REPORTED IN MASSACHUSETTS, 1908-1929, BY AGE AND SEX\*

| AGE                    | MALE | FEMALE | RATIO: MALES<br>TO 1 FEMALE |
|------------------------|------|--------|-----------------------------|
| Under 1 year.....      | 87   | 87     | 1.00                        |
| 1 year.....            | 232  | 163    | 1.42                        |
| 2 years.....           | 281  | 195    | 1.44                        |
| 3 years.....           | 216  | 176    | 1.22                        |
| 4 years.....           | 193  | 151    | 1.37                        |
| 5 years.....           | 162  | 128    | 1.26                        |
| 6 years.....           | 141  | 112    | 1.25                        |
| 7 years.....           | 111  | 98     | 1.13                        |
| 8 years.....           | 102  | 66     | 1.54                        |
| 9 years.....           | 65   | 53     | 1.22                        |
| 10 years.....          | 65   | 47     | 1.38                        |
| 11 years.....          | 54   | 49     | 1.10                        |
| 12 years.....          | 44   | 42     | 1.04                        |
| 13 years.....          | 41   | 37     | 1.10                        |
| 14 years.....          | 57   | 25     | 2.28                        |
| 15 years.....          | 47   | 21     | 2.23                        |
| 16 years.....          | 33   | 18     | 1.83                        |
| 17 years.....          | 30   | 16     | 1.87                        |
| 18 years.....          | 18   | 11     | 1.63                        |
| 19 years.....          | 15   | 16     | 0.93                        |
| 20 to 24 years.....    | 76   | 34     | 2.23                        |
| 25 to 29 years.....    | 33   | 29     | 1.13                        |
| 30 to 34 years.....    | 21   | 17     | 1.23                        |
| 35 to 39 years.....    | 15   | 17     | 0.88                        |
| 40 to 44 years.....    | 7    | 6      | 1.16                        |
| 45 to 49 years.....    | 3    | 5      | 0.60                        |
| 50 to 54 years.....    | 3    | 4      | 0.75                        |
| 55 to 59 years.....    | 2    | 2      | 1.00                        |
| 60 years and over..... | 1    | 1      | 1.00                        |

\* Forsbeck and Luther, New England J. Med. 203: 1117, 1930.

**Sex Incidence in Urban and Rural Outbreaks.** We have found no tendency for the sex ratio to vary consistently with density of population. There is apparently no significant difference between the urban and rural cases as regards sex.



**Explanations of Greater Incidence among Males.** No adequate reason for the greater incidence of poliomyelitis among males is known. A study of Table 64 reveals no obvious point in common among the high

TABLE 67

POLIOMYELITIS, NEW YORK CITY, 1916, SEX DISTRIBUTION OF CASES BY AGE PERIODS; NUMBER OF CASES, MALE AND FEMALE, WITH RATIO OF MALES TO FEMALES AT EACH AGE\*

| AGE                 | MALES | FEMALES | RATIO |
|---------------------|-------|---------|-------|
| Under 1 year.....   | 557   | 444     | 1.25  |
| 1 year.....         | 1,073 | 771     | 1.39  |
| 2 years.....        | 1,175 | 864     | 1.36  |
| 3 years.....        | 795   | 635     | 1.25  |
| 4 years.....        | 469   | 365     | 1.28  |
| 5 years.....        | 332   | 262     | 1.27  |
| 6 years.....        | 203   | 150     | 1.35  |
| 7 years.....        | 121   | 115     | 1.05  |
| 8 years.....        | 84    | 71      | 1.18  |
| 9 years.....        | 69    | 48      | 1.44  |
| 10 years.....       | 41    | 36      | 1.14  |
| 11 years.....       | 19    | 26      | 0.73  |
| 12 years.....       | 17    | 14      | 1.21  |
| 13 years.....       | 18    | 13      | 1.38  |
| 14 years.....       | 24    | 14      | 1.71  |
| 15 years.....       | 12    | 19      | 0.63  |
| 16 years.....       | 5     | 6       | 0.83  |
| 17 years.....       | 8     | 3       | 2.00  |
| 18 years.....       | 12    | 1       | 2.00† |
| 19 years.....       | 3     | 7       | 0.43  |
| 20 to 24 years..... | 19    | 11      | 1.73  |
| 25 to 29 years..... | 26    | 16      | 1.62  |
| 30 to 34 years..... | 11    | 6       | 1.83  |
| 35 to 39 years..... | 6     | 6       | 1.00  |
| 40 to 44 years..... | 3     | 2       | 1.50  |
| 45 to 49 years..... | 3     | 3       | 1.00  |
| 50 to 59 years..... | 1     | —       | —     |
| Unknown.....        | 214   |         |       |
| All ages.....       | 5,106 | 3,909   | 1.31  |

\* Lavinder, Freeman and Frost, Public Health Bull. 91: 233, 1918.

† As given.

ratios nor the low. There is no consistent increase of one sex with latitude or nationality (the low ratio of male to female deaths among negroes in the United States was mentioned, but the numbers thought too small to draw conclusions).

There is apparently no consistent time trend, although Forsbeck and Luther (F 57) pointed out that in their Massachusetts series, the proportion of males appears to be increasing. The 1931 epidemic in New York City also shows a higher proportion of males than did the 1916 epidemic in that city.

It has at times been suggested that the higher incidence in males is due to greater exposure. If, however, we assume greater exposure of

TABLE 68  
POLIOMYELITIS, NEW YORK CITY, 1931, CASES AND DEATHS BY AGE AND SEX\*

| AGE                    | CASES |        |       | DEATHS |        |       |
|------------------------|-------|--------|-------|--------|--------|-------|
|                        | Male  | Female | Ratio | Male   | Female | Ratio |
| 0 to 1 year.....       | 96    | 69     | 1.39  | 17     | 15     | 1.13  |
| 1 to 2 years.....      | 220   | 160    | 1.37  | 24     | 16     | 1.50  |
| 2 to 3 years.....      | 305   | 253    | 1.20  | 32     | 16     | 2.00  |
| 3 to 4 years.....      | 313   | 225    | 1.39  | 28     | 26     | 1.08  |
| 4 to 5 years.....      | 276   | 173    | 1.59  | 44     | 15     | 2.93  |
| 5 to 6 years.....      | 175   | 139    | 1.26  | 82     | 64     | 1.28  |
| 6 to 7 years.....      | 169   | 117    | 1.44  |        |        |       |
| 7 to 8 years.....      | 148   | 110    | 1.34  |        |        |       |
| 8 to 9 years.....      | 119   | 85     | 1.40  |        |        |       |
| 9 to 10 years.....     | 82    | 61     | 1.34  | 35     | 22     | 1.59  |
| 10 to 14 years.....    | 248   | 154    | 1.61  |        |        |       |
| 15 to 19 years.....    | 66    | 48     | 1.37  | 20     | 15     | 1.33  |
| 20 to 24 years.....    | 24    | 26     | 0.92  | 11     | 6      | 1.83  |
| 25 to 34 years.....    | 18    | 25     | 0.72  | 5      | 6      | 0.83  |
| 35 years and over..... | 11    | 3      | 3.66  | 4      | 1      | 4.00  |
| Unknown.....           | 93    | 89     | —     | —      | —      | —     |
| Total.....             | 2,363 | 1,737  | 1.35  | 302    | 202    | 1.49  |

\* These figures have been given to us through the courtesy of the New York City Health Department.

males in the younger ages to account for the greater incidence, we should expect to find a greater resulting immunity among males in the older ages, with a reversal of the sex ratio in these higher ages. This is not the case. The proportion of males is usually as great or greater after the sexual differentiation of puberty. This is clearly shown above in the deaths as recorded by the United States Census for the years 1916 to 1928, and in Chart XVI made by Jungeblut and Engle from these



figures. In Table 69, we give for several outbreaks the ratio of male to females cases before and after the age of 15. The proportion of males to females was greater in the higher age group with one exception, that of the New York City epidemic of 1931.

The question naturally arises as to whether the greater incidence in males is due to a real sex difference in susceptibility. The evidence

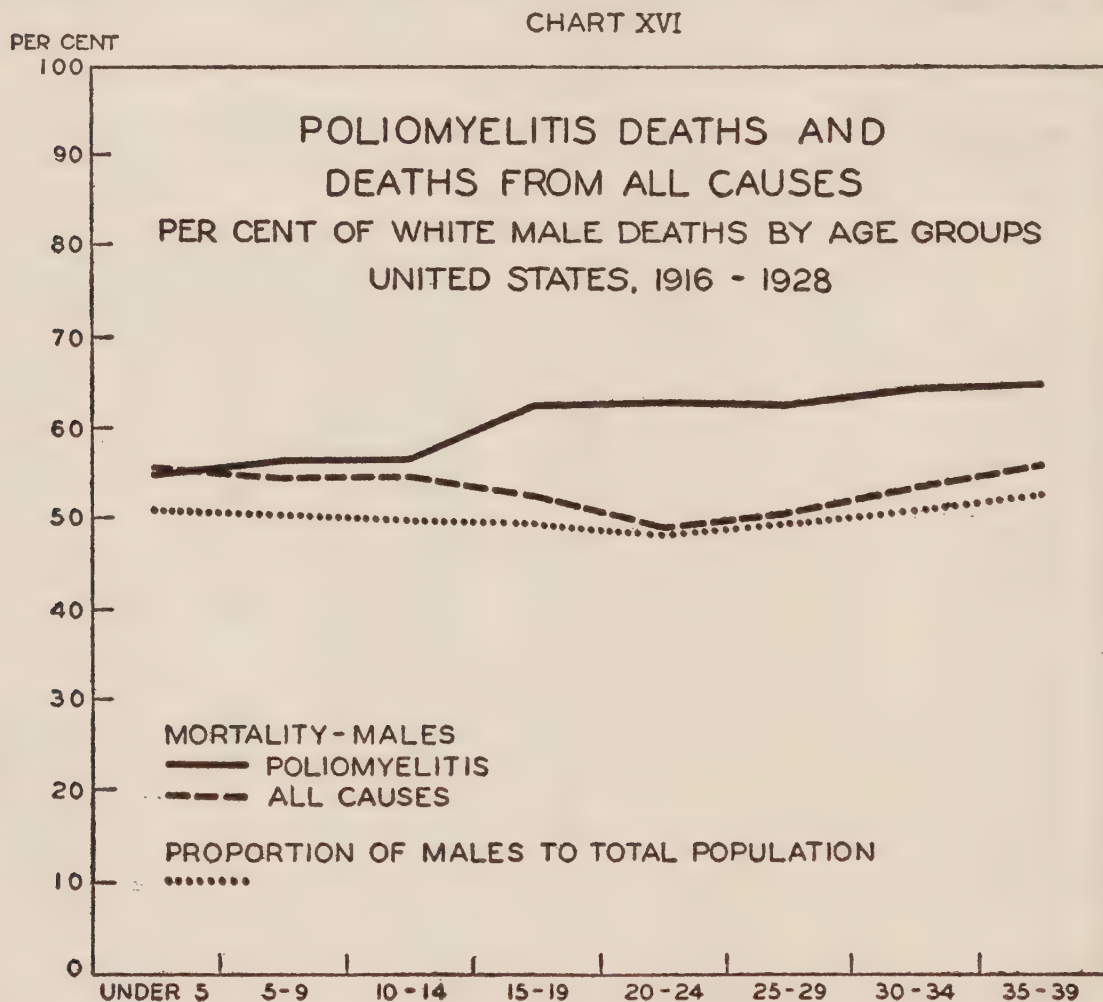


CHART XVI. Percentage of male deaths from poliomyelitis and from all causes with per cent of males in the general population. (Figures from United States Census Reports, 1916-1928. After Jungeblut and Engle.)

seems to indicate that it is. The very consistency with which more males are affected at all ages is an argument for considering it a real sex difference.

### Puberty, Menstruation and Pregnancy.

*Puberty.* A close analysis of the ratio between the sexes at the time of puberty is difficult. The reports giving the information are not numerous. Many reports give the age and sex incidence by individual

years for the first decade and by standard age groups thereafter. Moreover, the cases after the first ten years are few, and wide chance variation is possible. In some series of cases, however, there has been noticed a slight actual rise of cases at the time of puberty (and at times, a relative slowing up of the drop in the age curve, which is equivalent). Chart XI by Krahn, of the epidemic in Saxony in 1927 (K 23) shows this rise of cases at puberty plainly. While both sexes may show a small increase at puberty, the female curve shows it a little earlier than the male, as

TABLE 69

RATIO OF MALE TO FEMALE CASES IN VARIOUS OUTBREAKS OF THE 0-14 AND THE 15+ AGE GROUPS

| AUTHOR                                  | REFER-<br>ENCE | LOCATION                     | AGE  | CASES |        | RATIO:<br>MALES TO<br>1 FEMALE |
|-----------------------------------------|----------------|------------------------------|------|-------|--------|--------------------------------|
|                                         |                |                              |      | Male  | Female |                                |
| Frost                                   | F 71           | Iowa, 1910                   | 0-14 | 55    | 45     | 1.22                           |
|                                         |                |                              | 15+  | 75    | 25     | 3.00                           |
| Hill                                    | H 22           | Minnesota, 1909              | 0-14 | 56    | 44     | 1.27                           |
|                                         |                |                              | 15+  | 66    | 34     | 1.94                           |
| Forsbeck and Luther                     | F 57           | Massachusetts, 1908-<br>1929 | 0-14 | 1,851 | 1,429  | 1.29                           |
|                                         |                |                              | 15+  | 304   | 197    | 1.54                           |
| Lavinder, Freeman<br>and Frost          | L 16           | New York City, 1916          | 0-14 | 4,997 | 3,828  | 1.31                           |
|                                         |                |                              | 15+  | 109   | 81     | 1.35                           |
| New York City<br>Health Depart-<br>ment | *              | New York City, 1931          | 0-14 | 2,151 | 1,546  | 1.39                           |
|                                         |                |                              | 15+  | 119   | 102    | 1.17                           |

\* Personal communication.

would be expected. This results in a more close approximation of the ratio between the sexes at the time of female puberty, and a wider difference slightly later. The figures of Forsbeck and Luther in Table 66 illustrate this tendency.

*Menstruation.* Mention has elsewhere (*The Host, Neutralization of Normal Human Sera*) been made of the two instances reported by Jungeblut in which the sera of young women varied in power to neutralize before and after the menstrual period.

*Pregnancy.* In answer to a query as to poliomyelitis in preg-



nancy, the *Journal of the American Medical Association* (E 7) says: "Although there are no statistics available on the occurrence of poliomyelitis during pregnancy, some observers have the impression that the disease occurs in the later months of pregnancy more often than would be expected if it were only a chance coincidence. If this proves to be the case, it would suggest that some physiologic alteration during pregnancy may affect susceptibility."

Aycock (personal communication) has in the past two years encountered 10 cases of poliomyelitis in late pregnancy. He believes that this is out of proportion to what would normally have been expected, if the condition had not predisposed to the disease. He believes this indicates that susceptibility "may at times be due to a temporary stress on physiologic adaptation" (Practical Suggestions Regarding Poliomyelitis, American Medical Association, May, 1932).

There is a general impression that although the disease is likely to occur in the late months of pregnancy, it does not occur in the early months. We have met with no instances in the literature of the disease occurring in early pregnancy, but this is, of course, negative evidence. Jungeblut's series of neutralization tests done upon 10 women, pregnant from 3 to 7 months, all of whom neutralized, supports the impression.

#### RACE

The data on geographic and racial distribution of poliomyelitis are very limited. No comprehensive survey of either has ever, to our knowledge, been made. We can say that no absolute racial susceptibility or resistance to poliomyelitis has been demonstrated. No part of the world is known to be entirely free from it, and while marked differences in incidence are reported among the inhabitants of different countries, these differences are so complicated by other varying circumstances, such as climate or possibilities of exposure, that the ethnological factor is obscured.

The possibility of such a racial factor can best be tested where environmental factors are similar, and probably the nearest approach to this is found in the United States, with its diverse hereditary stocks. We have, therefore, considered the incidence among various races and nationalities from this point of view rather than from that of the geographic distribution.

#### Available Sources of Information.

*Morbidity.* The official morbidity reports in the United States are not made by race or nationality. The data available on morbidity

by race consist, therefore, only of special studies for various outbreaks. The difficulty of dealing with such data is easily seen,—incidence of disease depends upon both susceptibility and exposure, and for any attempt at a quantitative estimate of the former, the latter must be constant. Only over a period of years could exposure adjust itself for racial groups even when they live in close proximity.

*Mortality.* The mortality reports of the United States Census Bureau are made by color, the white and colored deaths being reported separately for the individual southern states, and a white and colored total for the entire registration area. Returns are made also separately for the Chinese, Japanese, and Indians but the deaths from poliomyelitis among those groups are so few that it is impossible to say more than that there is certainly no absolute resistance to the disease among these races.

**Negroes.** Since the information which we have on negroes, although meager, is more complete than for any other racial group, it is considered here in some detail. The fact must not, however, be lost sight of, that the negro in the United States does not represent a racially pure stock.

*Morbidity.* A number of outbreaks report a low incidence among the colored population. Francis (F 59) reports an outbreak in Texarkana in 1913:

|              | <i>Cases</i> | <i>Deaths</i> | <i>Fatality</i> |
|--------------|--------------|---------------|-----------------|
| White.....   | 124          | 8             | 6.4             |
| Colored..... | 19           | 7             | 36.8            |

In New York City in 1907, there were only 2 cases among negroes out of a total of 752 cases, although, if they had been in proportion to the population, there would have been 14 (C 19).

The New York City Health Department (N 20) reported upon the case and death rates for negroes and whites by age groups in the New York City epidemic of 1916. It will be noticed from Table 70 that the morbidity rate is higher for the whites in the age groups under 10 years, but that the mortality rate is higher for negroes. In the group over 10, the morbidity rate is lower for the negroes, and there were no deaths among them.

In New York City, in 1931, the attack rate for negroes was 0.22, for the white population 0.59 per 1000, the white rate being thus  $2\frac{1}{2}$  times as great as that for the colored. The mortality for the two races is not yet available. Neither the case nor death rates have as yet been reported by age groups.



TABLE 70  
POLIOMYELITIS, CASES AND DEATHS BY COLOR, AGE AND SEX; CASE AND DEATH RATE PER 1,000 ESTIMATED POPULATION AT  
DIFFERENT AGE GROUPS, CITY OF NEW YORK (JUNE 1 TO NOVEMBER 1, 1916)\*

|                        | WHITE      |        |       |       |        |      | NEGRO      |        |       |        |        |        |
|------------------------|------------|--------|-------|-------|--------|------|------------|--------|-------|--------|--------|--------|
|                        | Both sexes |        |       | Male  |        |      | Both sexes |        | Male  |        | Female |        |
|                        |            |        |       |       |        |      |            |        |       |        |        |        |
|                        | Cases      | Deaths |       | Cases | Deaths |      | Cases      | Deaths | Cases | Deaths | Cases  | Deaths |
| Total, all ages.....   | 8,805      | 2,372  | 5,000 | 1,385 | 3,805  | 987  | 109        | 34     | 61    | 23     | 48     | 11     |
| Rate per 1,000.....    | 3.83       | 1.03   | 4.35  | 1.20  | 3.31   | 0.86 | 2.41       | 0.75   | 2.94  | 1.11   | 1.97   | 0.45   |
| Under 1 year.....      | 967        | 413    | 522   | 232   | 447    | 181  | 15         | 10     | 11    | 8      | 4      | 2      |
| Rate per 1,000.....    | 18.50      | 7.90   | 19.71 | 8.76  | 17.34  | 7.82 | 13.70      | 9.13   | 19.39 | 14.10  | 7.58   | 3.79   |
| Under 5 years.....     | 6,977      | 1,868  | 3,987 | 1,110 | 2,990  | 758  | 79         | 29     | 46    | 18     | 33     | 11     |
| Rate per 1,000.....    | 28.33      | 7.58   | 32.00 | 8.91  | 24.56  | 6.23 | 23.88      | 8.77   | 28.79 | 11.26  | 19.31  | 6.44   |
| Under 10 years.....    | 8,386      | 2,240  | 4,767 | 1,313 | 3,619  | 927  | 102        | 34     | 60    | 23     | 42     | 11     |
| Rate per 1,000.....    | 18.22      | 4.87   | 20.57 | 5.67  | 15.83  | 4.05 | 17.48      | 5.83   | 21.57 | 8.27   | 13.76  | 3.60   |
| 10 years and over..... | 419        | 132    | 233   | 72    | 186    | 59   | 7          | —      | 1     | —      | 6      | —      |
| Rate per 1,000.....    | 0.23       | 0.08   | 0.25  | 0.08  | 0.20   | 0.06 | 0.18       | —      | 0.06  | —      | 0.28   | —      |

\* Monograph, New York City Health Department, 1917.

In Fort Worth, Texas, in the 1927 outbreak, Crouch (C 34) reports that of 58 cases none was noted among negroes. Watkins and McKenzie (W 5) say that in the Detroit epidemic of 1924, there were among negroes only 5 cases in a total of 300, although negroes comprised about one-twelfth of the city's population.

*Mortality.* The average death rate per 100,000 for the registration states for the years 1923 to 1927 (U 3) was for the white population 1.23 and for the colored 1.05. These figures are, however, not comparable, for the mass of colored population is in the South, where poliomyelitis is a relatively rare disease, and the mass of the white population is centered in the North where poliomyelitis is most prevalent.

The Mortality Statistics, United States Census Bureau, for 1923, contains a table (Table 71) of comparative rates per 100,000 for the whites and negroes for the Southern states for 1914 to 1923. Not all the states have records for all these years; the number of years from which the average is taken is given in the right-hand column.

An attempt to reconcile the apparent discrepancy in the morbidity and mortality figures would hardly be profitable. The mortality statistics appear to contradict the impression made by the morbidity figures that a difference between the races exists, at least in the South, where the death rates are approximately equal, the rate for the colored population being even slightly higher. What interpretation to put upon the low morbidity figures is a matter for speculation. It may be that they represent incomplete recording, especially in the South, where the difficulties that the negro presents to statisticians are well recognized. On the other hand, the problem in the North is complicated by immigration, which produces a disproportion of adult negroes in northern populations.

The factors productive of mortality, as Stallybrass (S 53) points out, are much more complex than the factors productive of morbidity, since mortality depends both upon prevalence and fatality. Thus, the discrepancy between morbidity and mortality figures may represent a high case fatality, which in turn may be due either to some peculiarity in racial response to the disease, or to poorer medical care due to the low economic status of the negro. Thus, in New York City in 1916 (Table 70) the case fatality for whites was 26.9, and for negroes 31.2. In Francis' figures for Texarkana in 1913 (see above) the case fatality was 6.4 for the whites, and 36.8 for the colored. If a high case fatality were the explanation, however, we should expect the relative mortality



to increase in the states farthest south where the economic status of the negro is probably lowest. This is not the case, the mortality being lowest for negroes in the Gulf States and increasing somewhat irregu-

TABLE 71

POLIOMYELITIS, DEATH RATES FOR WHITES AND NEGROES, SOUTHERN STATES, FOR THE AVAILABLE YEARS, 1914-1923\*

| STATE           | RATE PER<br>100,000 | RATIO:<br>WHITE RATE<br>TO COLORED | NUMBER OF<br>YEARS FROM<br>WHICH AVER-<br>AGES ARE MADE |
|-----------------|---------------------|------------------------------------|---------------------------------------------------------|
| Florida:        |                     |                                    |                                                         |
| White.....      | 0.66                | 1:0.72                             | 5                                                       |
| Colored.....    | 0.48                |                                    |                                                         |
| Georgia:        |                     |                                    |                                                         |
| White.....      | 1.25                | 1:0.80                             | 2                                                       |
| Colored.....    | 1.00                |                                    |                                                         |
| Kentucky:       |                     |                                    |                                                         |
| White.....      | 1.27                | 1:1.03                             | 10                                                      |
| Colored.....    | 1.32                |                                    |                                                         |
| Louisiana:      |                     |                                    |                                                         |
| White.....      | 0.75                | 1:0.68                             | 6                                                       |
| Colored.....    | 0.51                |                                    |                                                         |
| Maryland:       |                     |                                    |                                                         |
| White.....      | 1.88                | 1:1.53                             | 10                                                      |
| Colored.....    | 2.88                |                                    |                                                         |
| Mississippi:    |                     |                                    |                                                         |
| White.....      | 1.04                | 1:0.80                             | 5                                                       |
| Colored.....    | 0.84                |                                    |                                                         |
| North Carolina: |                     |                                    |                                                         |
| White.....      | 1.09                | 1:1.33                             | 10                                                      |
| Colored.....    | 1.46                |                                    |                                                         |
| South Carolina: |                     |                                    |                                                         |
| White.....      | 1.16                | 1:0.84                             | 8                                                       |
| Colored.....    | 0.98                |                                    |                                                         |
| Tennessee:      |                     |                                    |                                                         |
| White.....      | 1.01                | 1:1.32                             | 7                                                       |
| Colored.....    | 1.34                |                                    |                                                         |
| Virginia:       |                     |                                    |                                                         |
| White.....      | 1.81                | 1:0.84                             | 10                                                      |
| Colored.....    | 1.53                |                                    |                                                         |
| Average rate:   |                     |                                    |                                                         |
| White.....      | 1.19                |                                    |                                                         |
| Colored.....    | 1.33                |                                    |                                                         |

\* Mortality statistics, United States Census Bureau, 1923.

larly toward the border states where it is in excess of that for the whites (see Table 71).

Without more complete data, especially for the Northern states, where reporting and care are more nearly comparable among the two races, it is impossible therefore to determine whether this apparent difference is due to incomplete reporting, to a high case fatality, or to a difference inherent in the races. On the other hand, it must be remem-

TABLE 72

DEATHS UNDER 10 YEARS, ACCORDING TO NATIVITY OF MOTHER; DEATH RATE PER 1,000 ESTIMATED POPULATION NATIVITY OF MOTHERS OF CHILDREN UNDER 10 YEARS (JUNE 1 TO NOVEMBER 1, 1916)\*

| NATIVITY OF MOTHER     | DEATHS OF CHILDREN UNDER 10 YEARS | DEATH RATE PER 1,000 POPULATION OF CHILDREN UNDER 10 YEARS |
|------------------------|-----------------------------------|------------------------------------------------------------|
| Austria-Hungary.....   | 194                               | 1.67                                                       |
| Bohemia.....           | 13                                | 2.31                                                       |
| British America.....   | 12                                | 1.63                                                       |
| England.....           | 19                                | 1.38                                                       |
| France.....            | 2                                 | 0.69                                                       |
| Germany.....           | 102                               | 2.37                                                       |
| Ireland.....           | 158                               | 2.25                                                       |
| Italy.....             | 402                               | 1.63                                                       |
| Russia and Poland..... | 381                               | 1.71                                                       |
| Scotland.....          | 12                                | 2.44                                                       |
| Sweden.....            | 25                                | 2.52                                                       |
| Switzerland.....       | 4                                 | 2.66                                                       |
| United States.....     | 826                               | 2.42                                                       |
| Other Foreign.....     | 101                               | 2.69                                                       |
| Unknown.....           | 23                                | —                                                          |
| Total.....             | 2,274                             | 2.02                                                       |

\* New York City Health Department Monograph, 1917, p. 376.

bered also that the admixture of white blood is greatest in the north, and this would tend to conceal a racial resistance.

Negroes have been variously reported as resistant to other infections, although the evidence is somewhat contradictory, as it is in the case of poliomyelitis. Thus Doull (D 17), on the basis of studies made in Baltimore, reports low rates among negroes in diphtheria, both morbidity and mortality. He explains this as a real racial resistance, and not an antitoxic immunity. Emerson (E 14), on the contrary, found in New York City, 1921 to 1925, an apparently high death rate among negroes from diphtheria, although the scarlet fever rate was low.



**Difference in Incidence by Nationality.** The Monograph of the New York City Health Department gave, for the epidemic of 1916 in that city, a table of deaths and death rates of children under 10 years according to the nativity of the mother. These are given in Table 72. Similar data are not yet available for the 1931 epidemic.

Lavinder, Freeman and Frost (L 16) give morbidity rates by nationality in Richmond Borough, 1916. Their figures are given in Table 73.

TABLE 73  
NATIONALITY OF CASES, WITH INCIDENCE RATIO, PER 1,000 POPULATION; BOROUGH OF RICHMOND, NEW YORK CITY, 1916\*

|                                      | NUMBER OF<br>CASES | RACIAL STOCK,<br>POPULATION,<br>CENSUS 1910 | RATE PER<br>1,000 |
|--------------------------------------|--------------------|---------------------------------------------|-------------------|
| Americans (including 2 colored)..... | 138                | 29,456                                      | 4.5               |
| Italian extraction.....              | 41                 | 7,662                                       | 5.3               |
| German.....                          | 23                 | 13,959                                      | 1.7               |
| Russian.....                         | 23                 | 3,378                                       | 6.8               |
| Irish.....                           | 15                 | 13,700                                      | 1.1               |
| Scandinavian.....                    | 15                 | 3,427                                       | 4.3               |
| English.....                         | 13                 | 4,385                                       | 2.9               |
| Austrian.....                        | 12                 | 1,656                                       | 7.2               |
| Scotch.....                          | 1                  | 1,285                                       | 0.7               |
| Not listed.....                      | 9                  | —                                           | —                 |
| Suspicious cases excluded.....       | 290                | —                                           | —                 |
| Rate per 1,000 for the borough.....  | 3                  | —                                           | —                 |

\* Lavinder, Freeman and Frost, Public Health Bulletin, 91, 1918.

It will be seen that the variations in incidence as between the different nationalities shed no light. It has been an interesting coincidence, though probably nothing more, that in Buffalo in 1912 (Frost, F 71), in New York City in 1916 (Lavinder, Freeman and Frost, L 16), and in New York City in 1931, the epidemics have appeared first among the Italians.

**Are Racial Variations in Percentage of Blood Groups a Factor in Susceptibility?** The Hirshfelds pointed out some years ago that there were variations in the incidence of serological types in different races. Since persons in the various blood groups apparently show a difference

in susceptibility to poliomyelitis, Jungeblut and Smith (J 27) suggested that there may be a correlation between the two. No study of geographic or racial distribution of poliomyelitis from this point of view has been made, however.

#### CONSTITUTIONAL FACTORS INFLUENCING HOST RESISTANCE

Susceptibility to poliomyelitis has been shown to vary with age, with sex, possibly with race. None of these discussions have, however, answered the fundamental problem: why, of two persons, the same age, the same sex, the same race, living side by side under similar environmental conditions, one (numerically speaking, the more normal) should react with an immunity response to initial infection with the virus, while the other develops the clinical disease. Even among those who react clinically, why do some escape without paralysis while others do not?

There is no test by which persons who are susceptible to poliomyelitis may be distinguished from those who are not, except the failure of their serum to neutralize. This failure has been ordinarily interpreted as indicating susceptibility. This test is expensive, involving the use of a monkey for each serum tested, and is prohibitive for extensive tests. No great number of persons is, therefore, known to be susceptible. Even of those who have been so tested, no study has been reported of the constitutional difference between those who do and those who do not neutralize.

Attempts, therefore, to detect differences in individuals which may account for the susceptibility of persons to poliomyelitis consist of estimations of deviations from the normal in the clinical cases.

**Susceptibility or Resistance May Be Local.** Amoss (A 19) points out that natural resistance to the virus of poliomyelitis may be due in part to local mechanisms of defense:

- (a) neutralizing power of nasopharyngeal secretions,
- (b) impermeability of the nasal mucosa,
- (c) continuity of the meningeal-choroidal plexus.

(a) The presence of a substance possessing the power of neutralizing or otherwise destroying the virus in the washings of the nasopharyngeal mucous membrane of healthy persons was demonstrated by Amoss and Taylor (A 24). The neutralizing power diminishes or disappears when inflammation of the mucous membrane is present. This neutralizing capacity of the normal nasal secretions constitutes the individual's first line of defense.



(b) Permeability or impermeability of the nasal mucosa, whether morphological or functional, may determine the outcome of infection. It has been suggested that such permeability may decrease with age, and may offer an explanation for at least a part of the increase with age of nonspecific resistance to poliomyelitis. The Medical Research Council (G 16b) quote Renault and Lévy (R 5) as considering that in diphtheria an intact condition of the mucous membranes may play as important a part in protection as antitoxin in the blood.

The observations of Aycock and Luther (A 50) are interesting in this regard. They report that 36 patients (out of 714 analyzed) gave a history of tonsillectomy within a year, 16 of these within one month. Every one of these 16 had had the operation performed between 7 and 18 days prior to the onset of the disease.

This time interval, which tallies with the probable incubation period of poliomyelitis, points to the lacerated mucosa as facilitating the entry of the virus, probably already present.

(c) A third line of defense consists in the continuity of the meningeal-choroidal plexus, the normal barrier separating the nervous system from the blood infections. Flexner and Amoss (F 22) showed that infection of monkeys with poliomyelitis virus by the blood stream, a route ordinarily closed, could be accomplished after intraspinal injection of a foreign protein setting up an aseptic meningitis. Infection by the nasal route was rendered easier by similar preparation.

Such a method of localization is not peculiar to poliomyelitis. Sawyer and Lloyd (S 7), for example, have recently shown that intraperitoneal infection of mice with the virus of yellow fever, and the simultaneous injection of starch solution into the brain, will cause a localization of the virus, the mice dying of yellow fever encephalitis.

#### **Endocrine Abnormality.**

*Morphological Characteristics.* Draper (D 18) was the first to suggest that susceptibility to poliomyelitis might lie in an endocrine imbalance.

In the course of his clinical observations during the New York epidemic of 1916, he noted that individuals displaying certain definite morphological characteristics recurred with insistent frequency among his patients. During the 1931 epidemic in New York City, he has continued his observations, and has reiterated his belief (D 19a) that a particular type is as necessary to the disease as is the virus—"it must be equally specific." Since his earlier observations are included in his 1932 paper, only the latter is summarized here. In it he has at-

tempted a quantitative estimation of these physical characteristics and their correlation with hormonal imbalance. He reports a comparison between 74 poliomyelitis patients, and a control series of 122 hospital patients with miscellaneous diseases, and concludes as to the deviations of the poliomyelitis patients from the controls:

1. Their faces have a broad, wide-eyed expression.
2. There is usually a definite over-bite, and frequently a maxillary prognathism.
3. The gonial angle is more obtuse than in the controls.
4. The subcostal angle is narrower than in the controls.
5. There is a tendency to gain weight, the subjects of poliomyelitis being often pudgy, fat types.
6. The hand index shows a short, broad form.
7. The pelvis is definitely wide as compared with the shoulders.
8. The external genitalia are small; certain abnormalities also appear, one-sided crypt-orchidism or incompletely descended testes.

He also lists certain features, without giving definite measurements:

1. Nail lunulae are less frequent than in controls.
2. A mongoloid trend is seen in the palpebral fissure and the not infrequent presence of an epicanthal fold. By mongoloid he means a peculiar, smooth, downward curving slant of the inner half of the arcs of the upper eyelid, which he believes to be almost universal in poliomyelitis patients. This is not to be confused with the arrangement in which the inner canthus is placed lower than the outer, when there is produced the downward and inward slant of the whole eye slit, though this may also be present.
3. Pigmentation of the skin is frequently observed.
4. Spacing of the teeth, and other irregularities of dentition are commonly found.
5. The general picture known as status lymphaticus is often seen.

He concludes: "Thus it appears that the constitutional structure of the infantile paralysis people points strongly to deficiencies of the three glands, namely, the pituitary, gonad and adrenal cortex. What the significance of the lymphatism and the mongoloid trend may be is still unexplained. . . . In conclusion, it may be said that this highly specialized type of child is a causal factor in the occurrence of infantile paralysis, of equal importance with the virus; but so far as the development of paralysis is concerned, the constitution of the child is of greater significance than the virus."



Opinions among clinicians as to these peculiarities of appearance vary from a denial of their presence to a partial acceptance. We know of no statement in the literature which can be taken as an unreserved endorsement of Draper's findings. Neal, with an extraordinarily wide experience with the disease, sees in the physical makeup of the patients nothing peculiar to them. Macnamara, in Australia, likewise sees nothing characteristic in the appearance of the patients.

Following the 1931 epidemic in New York City, an attempt was made by Levine, Park and Neal (personal communication) to verify some of Draper's observations. Fifty-two paralyzed children still remaining in convalescent institutions, matched by 52 controls of similar age, sex and race, were studied as to (1) separation of teeth, (2) epicanthal folds, (3) complexion, (4) nail lunulae, (5) pigmented spots. Their results which are given below failed to confirm Draper's findings; they likewise found no evidence of mongoloid eyes occurring more frequently in those having poliomyelitis.

|                          | <i>Poliomyelitis<br/>Cases</i> | <i>Controls</i> |
|--------------------------|--------------------------------|-----------------|
| <i>Teeth:</i>            |                                |                 |
| Together.....            | 29                             | 23              |
| Separated.....           | 19 (36%)                       | 23 (46%)        |
| No teeth.....            | 4                              | 3               |
| <i>Epicanthal folds:</i> |                                |                 |
| Normal.....              | 27                             | 22              |
| +.....                   | 17                             | 13              |
| ++.....                  | 6                              | 7               |
| +++.....                 | 2                              | 7               |
|                          | (48%)                          | (55%)           |
| <i>Color:</i>            |                                |                 |
| Blonde.....              | 32                             | 22              |
| Brunette.....            | 18 (34%)                       | 25 (50%)        |
| Colored.....             | 2                              | 2               |
| <i>Lunulae:</i>          |                                |                 |
| None.....                | 23 (44%)                       | 22 (45%)        |
| Very few.....            | 22                             | 20              |
| More than 4 present..... | 7                              | 7               |
| <i>Pigmented spots:</i>  |                                |                 |
| None.....                | 17                             | 13              |
| Few.....                 | 25                             | 28              |
| Moderate.....            | 7                              | 3               |
| Many.....                | 1                              | 3               |
| Colored.....             | 2                              | 2               |

*Weight of Patients.* Draper's suggestion that the victims of poliomyelitis were frequently "fat, pudgy types" raises the question of the weight of patients.

The early writers on poliomyelitis emphasized the fact that it was the robust, healthy child, rather than the undernourished, sickly child who developed the disease. It is interesting to note that Heine (H 18) who in 1840 first described the acute stage of poliomyelitis called attention to the previous excellent health and "blooming appearance" of the pa-

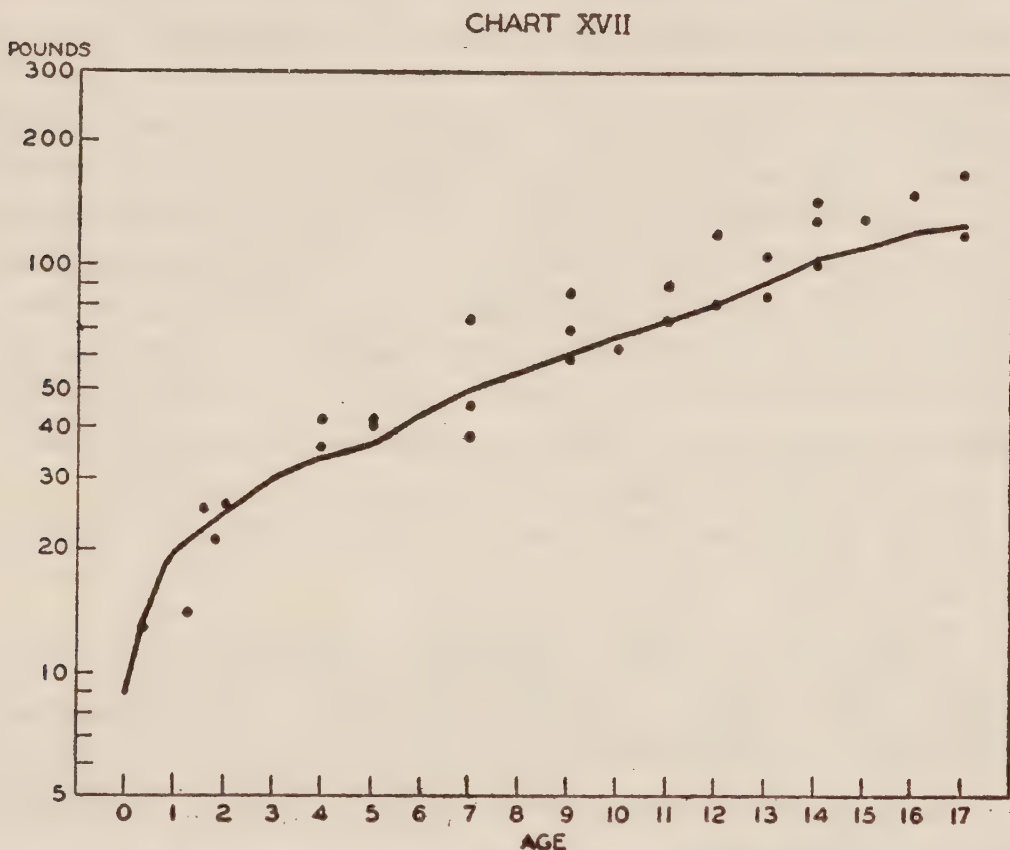


CHART XVII. Weight of 29 individuals attacked with poliomyelitis compared with average weight for the same age. Continuous line represents average weight curve. (From Aycock, J. Prev. Med. 3: 245, 1929.)

tients. The statement is often met in the literature that nutrition, in the sense of general undernourishment, is not a factor in poliomyelitis. It is not a disease of the poorer classes, among whom undernourishment is common. Müller (M 55) cites the fact that during the World War, the disease did not become epidemic in Germany, indicating that lack of strength and nourishment does not predispose to poliomyelitis.

The only data that we have been able to find on weight are those of Aycock (A 36). In Chart XVII is shown his comparison of the weight



of 29 patients "at the time of the occurrence of poliomyelitis," with the normal weight curve for similar ages. He has presented these, "not as proof that the disease does occur in individuals who are overweight, (the number of observations is too small) but as an indication of the desirability of further studies along this line."

Dr. Jean Macnamara has told us that her observations in Australia lead her to believe that the patients when attacked are usually normal. Some cases gain weight after paralysis, but she attributes this to a higher caloric diet than is justified by the patient's inactive life. Restriction of the diet, and muscle reëducation easily control the excessive deposition of fat.

*Autarcesis, Physiological Variation due to Seasonal Adjustment of the Host.* Aycock believes that the type of individual affected suggests an endocrine imbalance. From comparative studies of the distribution of immunity and the distribution of the disease, considered from the point of view of concentration of population, age, climate and season, he (A 36) concluded that variations in the occurrence of the disease might be related to the effects of climate and season on the host. He suggests that there may be some variation in the physiological activity of the body which influences resistance to poliomyelitis. To distinguish such resistance from specific immunity, he suggests the word *autarcesis*.

Such seasonal and climatic variations in physiological activity he does not consider abnormal or pathological, but in the nature of normal adjustment of the body to varying environment. Any relation between such variation and susceptibility to disease would lie not in such adjustment, but in a failure to adjust in some respect, creating an imbalance or "deficiency" in the body.

*Sex Incidence.* The fact that males are, at all ages, more susceptible to poliomyelitis than females, and the slight evidence which we have that indicates that susceptibility to poliomyelitis may be increased at times of sexual inequilibrium, i.e., puberty and late pregnancy, points toward an endocrine factor in susceptibility. This has been considered under *Sex*.

*Experimental Evidence.* Jungeblut and Engle (J 22) have approached the problem of resistance to poliomyelitis as influenced by endocrine balance from the experimental side. They have found some evidence that the resistance factor may be connected with a secretion of the anterior pituitary gland. They were able, in a small number of instances, to protect immature monkeys against intracerebral inocula-

tion of the virus of poliomyelitis with anterior pituitary extracts or implants, although the success has not been uniform.

**Varying Susceptibility of Blood Groups.** The possibility that persons belonging to the four blood groups, as divided according to their inter-agglutinating reactions, may vary in susceptibility to poliomyelitis, has recently attracted attention. The first reports on blood groups were made during the 1927 Roumanian outbreak. Some confusion, whether of systems of grouping or otherwise, has resulted in conflicting reports on these results. Manicatide, Brătescu, and Rucescu (M 15) state that Marinesco and Drăganescu studied the blood groups and established the fact that the most frequent types were of groups I and II and are quoted in the literature to that effect. Marinesco, Manicatide, and Drăganescu (M 19), however, say that groups II and IV predominated in the 55 cases to which they applied the test. They do not give the number of cases in each group.

Grooten and Kossovitch (G 18) tested 78 poliomyelitic children in Strasbourg in the Alsatian epidemic of 1930. They obtained the following figures:

|                              | <i>Blood Groups</i> |          |          |           |
|------------------------------|---------------------|----------|----------|-----------|
|                              | <i>O</i>            | <i>A</i> | <i>B</i> | <i>AB</i> |
| Poliomyelitis, per cent..... | 29.1                | 56.4     | 14.5     | 0         |
| Normal, per cent.....        | 37.7                | 39.6     | 16.9     | 5.6       |

It will be noted that there is an increase in the A group, a decrease in the O group, and a complete absence of the AB group. They observed the same changes in cancer, but the opposite in tuberculosis, in which the AB group was appreciably increased.

Foà (F 55) also tested a small series, 22 poliomyelitic children in Turin and Savoy. Comparing his results with those obtained by Mino on healthy Piedmontese, he reports:

|                                    | <i>O</i> | <i>A</i> | <i>B</i> | <i>AB</i> |
|------------------------------------|----------|----------|----------|-----------|
| Cases.....                         | 9        | 12       | 1        | 0         |
| Poliomyelitis, per cent.....       | 40.9     | 54.6     | 4.5      | 0         |
| Healthy Piedmontese, per cent..... | 41.8     | 43.5     | 11.5     | 3         |

During the 1931 epidemic in New York City, Jungeblut and Smith (J 27) made the most extensive study of blood groups in poliomyelitis that has so far been reported. In view of the wide fluctuation in the severity of the disease, they considered the blood groups not only in relation to general morbidity, but also in relation to the extent of paralysis, and to mortality. They report upon a total of 578 sera taken



TABLE 74  
INCIDENCE OF BLOOD GROUPS AMONG VARIOUS GROUPS OF CASES OF POLIOMYE-  
LITIS AND 1,000 NORMAL PERSONS\*

|                                                                                                                               | TOTAL | O    | A    | B    | AB   |
|-------------------------------------------------------------------------------------------------------------------------------|-------|------|------|------|------|
| I. Normal sera, transfusion records,<br>Presbyterian Hospital New York<br>City:                                               |       |      |      |      |      |
| Number.....                                                                                                                   | 1,000 | 456  | 357  | 140  | 47   |
| Per cent.....                                                                                                                 | 100   | 45.6 | 35.7 | 14.0 | 4.7  |
| II. Polio-convalescent sera, mostly from<br>the 1916 epidemic in New York<br>City and State:                                  |       |      |      |      |      |
| Number.....                                                                                                                   | 208   | 108  | 69   | 14   | 17   |
| Per cent.....                                                                                                                 | 100   | 51.9 | 33.2 | 6.7  | 8.2  |
| III. Poliomyelitis cases (abortive and<br>paralytic) during the 1931 epi-<br>demic, Willard Parker Hospital:                  |       |      |      |      |      |
| Total:                                                                                                                        |       |      |      |      |      |
| Number.....                                                                                                                   | 303   | 126  | 124  | 38   | 15   |
| Per cent.....                                                                                                                 | 100   | 41.6 | 40.9 | 12.5 | 5.0  |
| Paralytic (exclusive of fatal):                                                                                               |       |      |      |      |      |
| Number.....                                                                                                                   | 188   | 84   | 77   | 20   | 7    |
| Per cent.....                                                                                                                 | 100   | 44.6 | 40.9 | 10.6 | 3.7  |
| Under 5 years:                                                                                                                |       |      |      |      |      |
| Number.....                                                                                                                   | 120   | 55   | 47   | 15   | 3    |
| Per cent.....                                                                                                                 | 100   | 45.8 | 39.1 | 12.5 | 2.5  |
| 5 to 10 years:                                                                                                                |       |      |      |      |      |
| Number.....                                                                                                                   | 46    | 19   | 20   | 5    | 2    |
| Per cent.....                                                                                                                 | 100   | 41.3 | 43.5 | 10.8 | 4.4  |
| Over 10 years:                                                                                                                |       |      |      |      |      |
| Number.....                                                                                                                   | 22    | 10   | 10   | 0    | 2    |
| Per cent.....                                                                                                                 | 100   | 45.5 | 45.5 | 0    | 9.0  |
| IV. Paralytic cases occurring in persons<br>over 5 years of age, cared for in<br>various hospitals in New York<br>City, 1931: |       |      |      |      |      |
| Number.....                                                                                                                   | 125   | 68   | 42   | 7    | 8    |
| Per cent.....                                                                                                                 | 100   | 54.4 | 33.6 | 5.6  | 6.4  |
| V. Fatal cases, Willard Parker Hos-<br>pital:                                                                                 |       |      |      |      |      |
| Under 5 years:                                                                                                                |       |      |      |      |      |
| Number.....                                                                                                                   | 7     | 2    | 2    | 2    | 1    |
| Per cent.....                                                                                                                 | 100   | 28.6 | 28.6 | 28.6 | 14.2 |
| Over 5 years:                                                                                                                 |       |      |      |      |      |
| Number.....                                                                                                                   | 20    | 10   | 7    | 1    | 2    |
| Per cent.....                                                                                                                 | 100   | 50.0 | 35.0 | 5.0  | 10.0 |

\* Jungeblut and Smith, J. Immunology, 23: 35, 1932.

partly from recent cases of the 1931 epidemic and partly from cases of former epidemics. We have summarized their results in Table 74.

It will be seen from Table 74, that the incidence of blood groups in cases of paralytic poliomyelitis under 5 years of age shows no marked deviation from the normal figures.

The deficiency of the B group among the paralytics over 5 years and the fatal cases is highly suggestive of some factor conferring resistance to members of that group. Eliminating the B group, the distribution of the other groups among the paralytics agrees with their distribution among the population at large within the probability of variation due to sampling groups of this size. There is no evidence of any selective factor conferring resistance or susceptibility upon members of the three remaining groups.

Under *Neutralization of the Virus*, we have given Jungeblut's results on neutralization of the virus by normal sera, classified by blood groups. It will be seen that the sera of members of the B group not only neutralized more frequently than any other group, but the pooled B sera neutralized in higher titer than any other group, a fact which strengthens their conclusion that there is some selective factor at work in the B group.

**The Inheritance Factor.** The factor of inheritance is frequently mentioned in the literature. Usually, however, this has reference to the simultaneous occurrence of the disease among siblings. Not infrequently instances are mentioned where a number of members of a family develop poliomyelitis. These instances are exceedingly interesting individually. They are not necessarily, however, due to an inherited predisposition to the disease, since the unusual incidence might have been due to a lack of previous exposure to the virus on the part of older members, and consequent lack of immunity. Thus, MacNalty (M 10) visited in Hertfordshire a family in September, 1926, of which 5 members had the disease. Everhardt and Cole (E 20) report an interesting family history; a family of 7, 5 of whom had it. Wickman (W 21) reported a family, of which 8 members suffered from the disease during the Swedish epidemic of 1905.

More suggestive of a real inherited increased susceptibility are the situations where older members of the family have the disease, and years later younger ones also develop it. Wickman (W 21) says that he and Fürntratt (F 72) had observed patients whose relatives (uncle and aunt) had previously been affected by poliomyelitis.

Dubois (D 22; D 23) concluded from his observations in Zürich that



predisposition to poliomyelitis is specific and inherited: "A nervous disposition, or susceptibility to other nervous disorders is, according to my observations, of no account. On the contrary, there seems to exist a special and certain disposition to poliomyelitis. Very often you find that parents, grandparents, or near relatives have suffered from this disease." In 310 cases, in which the family history could be obtained there had been a previous case of poliomyelitis,

3 times in a maternal aunt,  
3 times in a paternal uncle,  
once in the father,  
once in the grandfather,  
6 times in brothers or sisters.

Boul (B 23) quotes an instance of this in the Grays Thurrock epidemic of 1926, where the father of two of the patients had a residual paralysis in one leg, having himself been a victim of the disease 5 years previously.

Macnamara (personal communication) had met in Australia, the following instances of second cases in families at long intervals: in one family a boy suffered from the disease in 1928 and a girl in 1930; in another, one boy was affected in 1918 and one in 1930; in a third, one boy in 1918 and one in 1931.

These instances, of course, at once suggest the possibility of a chronic carrier in the families so affected. Aycock (paper read before the American Epidemiological Society, April 8, 1932), however, encountered an instance where such a possibility could be eliminated. Three brothers were, in infancy, adopted into different families in different localities, and did not subsequently meet. One developed poliomyelitis when about 4 years of age, another some years later when about 20 years of age.

Crouch (C 34) reports an instance of the children of three brothers and one sister being struck with poliomyelitis during the same summer. One of the brothers lived in California, and the only communication between him or his family and the other members of the family, who all lived in Fort Worth, Texas, was by letter.

#### NEUTRALIZATION TESTS UPON THE SERA OF NORMAL INDIVIDUALS

Under *Immunity*, there has been discussed the fact that the serum of recovered cases of poliomyelitis, of persons in contact with cases, and of many persons who have never, so far as is known, been in contact with a case of the disease, will, when mixed with the virus, neutralize its effect when injected into monkeys. Because of the epidemiological

significance which attaches to the neutralization of the virus by the sera of "normal" persons, the results which have been reported by various workers are given here in some detail. The interpretation which is to be placed upon these results is discussed under Latent Immunization.

Anderson and Frost, 1911, (A 26) were first to detect neutralization bodies in the serum of normal persons. They tested 3 normal adults and 2 normal children, the ages of whom are not given. They found that when they used a 1 per cent emulsion of virus, 1 adult clearly neutralized, the sera of the 2 children probably neutralized (the results were somewhat doubtful), while 2 adults did not. When they used a 5 per cent emulsion of virus, none of the sera neutralized. Since sera from recovered cases had, in their experience, neutralized a 5 per cent emulsion of virus, they concluded that, while the sera of normal persons might contain neutralizing substances, "the action has quantitative limits which clearly differentiate it from the action exercised by the serum of persons who have had poliomyelitis." These authors added to both the convalescent and normal sera to be tested, normal human serum. As the normal serum added in the above series was reported in their results as one which did not neutralize, it would not seem that their results were vitiated.

Peabody, Draper and Dochez (P 7) reported, in 1912, that, in view of the results of Anderson and Frost, which threw doubt upon the reliability of the neutralization test for purposes of diagnosis, that they had tested the sera of 4 normal adults, 2 physicians and 2 nurses, all in attendance upon poliomyelitis cases. Three neutralized and one did not. They also tested 2 children who were in the hospital for other causes: one 8 years old, which neutralized; one  $2\frac{1}{2}$  years old, which did not.

Kling and Levaditi (K 12) reported neutralization experiments with sera from 7 contacts, age not given, and 2 normal infants, in the Swedish epidemic of 1912. Of the 7 contacts, 2 completely neutralized, 4 partially neutralized (prolonged incubation period), and 1 failed to neutralize. The serum of 1 of the 2 normal infants, aged 2 years, did not neutralize; that of the other, aged 14 months, almost completely neutralized, again as indicated by a prolonged incubation period—32 days. In discussing these results with normal contacts, they stated very clearly the opinion that the immunity resulted from latent infection, the organism reacting to the virus only by the production of antibodies, or possibly in some instances, immunity followed an undiagnosed abortive form of the disease.



Leake (L 18) reported that of the sera from 3 normal adults tested, 1 a contact, neutralized the virus, while 2, not in contact with the disease, did not neutralize.

Aycock and Kramer, 1930, (A 46) tested 75 individuals of varying ages, the largest series so far reported. Forty-six of these were residents of urban communities, for the most part in or near Boston. The remaining 29 had spent their lives in rural districts, many of them on isolated farms so that they represented a greater degree of "ruralism" than is ordinarily encountered. Their results are summarized in Table 75.

The numbers tested in each age group are not, of course, large enough for close analysis. The authors have, however, noted that the virus

TABLE 75  
NEUTRALIZATION TEST FOR IMMUNITY TO POLIOMYELITIS WITH NORMAL HUMAN SERUMS, BY AGE GROUPS\*

| AGE                 | URBAN  |              | RURAL  |              |
|---------------------|--------|--------------|--------|--------------|
|                     | Number | Neutral-ized | Number | Neutral-ized |
| 0 to 4 years.....   | 12     | 5            | 4      | 0            |
| 5 to 9 years.....   | 10     | 8            | 8      | 0            |
| 10 to 14 years..... | 9      | 6            | 8      | 2            |
| 15 to 19 years..... | 7      | 6            | 4      | 2            |
| Adults.....         | 8      | 7            | 5      | 2            |
| Total.....          | 46     | 32           | 29     | 6            |

\* Aycock and Kramer, J. Prev. Med. 4: 189-200, 1930.

was neutralized in a larger proportion of sera from the older age groups than from the younger ones in both urban and rural individuals. In every age group, moreover, the urban sera neutralized the virus more frequently than did the rural sera.

Simultaneously with this report, Shaughnessy, Harmon, and Gordon published a preliminary and later a more complete report (S 33) on the quantitative antiviral content of convalescents, contacts, and normal persons, from Chicago, rural Illinois, Winnepeg, and the Virgin Islands. They tested the sera from 48 different persons: 14 convalescents; 3 persons from the Virgin Islands who had had an illness suggesting poliomyelitis; 6 familial contacts of poliomyelitis patients; 10 normal adults, including 1 from the Virgin Islands; 10 normal children, 6 ur-

ban and 4 rural; and 5 normal infants. These results are summarized in Table 76.

These results are especially interesting and significant. They show that, while serum from persons who have recovered from an attack of poliomyelitis possesses some power to neutralize the virus *in vitro*, the titer of antibodies in the serum of certain "normal" adults, both contacts and non-contacts may not only equal but appreciably exceed that of convalescents. They conclude that the power of neutralization develops gradually so that the majority of adults are immune. It will be

TABLE 76  
SUMMARY OF EXPERIMENTS WITH 48 HUMAN SERUMS FROM ILLINOIS, BOSTON,  
WINNIPEG AND THE VIRGIN ISLANDS\*

| HISTORY OF PERSONS SUPPLYING SERUM                                                                               | SERUMS<br>TESTED | SERUMS NEUTRALIZING<br>IN DILUTION |      |      |
|------------------------------------------------------------------------------------------------------------------|------------------|------------------------------------|------|------|
|                                                                                                                  |                  | 1:2                                | 1:10 | 1:30 |
| Poliomyelitis 6 months to 2 years before test . . .                                                              | 7                | 4                                  | 3    | 2    |
| Poliomyelitis 3 to 7 years before test . . . . .                                                                 | 4                | 2                                  | 2    | 2    |
| Poliomyelitis more than 10 years before test . . . .                                                             | 3                | 2                                  | 0    | 1    |
| Paralysis, possibly poliomyelitis, 2 years pre-<br>viously, Virgin Islands, aged 10, 14 and 19<br>years. . . . . | 3                | 1                                  | 2    | 0    |
| Family contacts of poliomyelitis patients . . . . .                                                              | 6                | 4                                  | 3    | 4    |
| Normal adults, 22 to 29 years old . . . . .                                                                      | 9                | 8                                  | 8    | 4    |
| Normal adult, Virgin Islands . . . . .                                                                           | 1                | 1                                  | 1    | 1    |
| Normal city children, 4 to 11 years old . . . . .                                                                | 6                | 5                                  | 5    | 5    |
| Normal rural children, 6 to 9 years old . . . . .                                                                | 4                | 1                                  | 1    | 0    |
| Normal infant, 7 weeks old . . . . .                                                                             | 1                | 1                                  | 1    | 1    |
| Normal infant, 6 months old . . . . .                                                                            | 1                | 1                                  | 0    | 0    |
| Normal infants, 9, 12 and 20 months . . . . .                                                                    | 3                | 0                                  | 0    | 0    |

\* Shaughnessy, Harmon and Gordon, J. Prev. Med. 4: 463-475, 1930.

seen from their tests that sera from normal infants between 6 months and 2 years of age were almost devoid of neutralizing properties, although the serum of a 7 week old infant neutralized actively.

Fairbrother and Brown (F 5) report a small series of neutralization tests upon children in a private boarding school, about 6 months following a small outbreak of bulbar poliomyelitis. The tests were made upon 5 convalescents, 3 of them pooled; 4 other children who were in the school at the time of the outbreak, 2 of whom were in close contact with cases and 2 of whom were not; 2 children who entered the school



after the outbreak; and a 3 month old baby. The 3 latter had never so far as known been in contact with the disease. The results are summarized in Table 77. It will be seen that the serum of every child tested, who was in the school at the time of the outbreak, neutralized, while of the 2 who entered after the outbreak, 1 did and 1 did not. The serum of the 3 month old baby apparently partially neutralized. These results are comparable to those of Dudley (D 28) in diphtheria.

TABLE 77  
NEUTRALIZATION TESTS UPON CHILDREN: CONVALESCENTS, CONTACTS AND NON-CONTACTS\*

|                                   | SERUM | AGE               | NATURE OF CASE             | RESULT                        |
|-----------------------------------|-------|-------------------|----------------------------|-------------------------------|
| In school at time of outbreak     | A     | 13 years          | Convalescent               | 0                             |
|                                   | B     | 11 years          | Convalescent               |                               |
|                                   | C     | 9 years           | Convalescent               |                               |
|                                   | D     | 7 years           | Convalescent               |                               |
|                                   | E     | 9 years           | Abortive case              | 0                             |
|                                   | F     | 8 years           | Brother of B—close contact | 0                             |
|                                   | G     | 13 years          | Brother of A—close contact | 0                             |
|                                   | H     | 10 years          | Contact—remote             | 0                             |
|                                   | I     | 8 years           | Contact—remote             | 0                             |
| Not in school at time of outbreak | J     | 9 years           | Never in contact           | 0                             |
|                                   | K     | 7 years           | Never in contact           | + (5 days)                    |
|                                   | L     | 3 months          | Never in contact           | + (11 days)                   |
|                                   |       | 2 saline controls |                            | 5 and 6 day incubation period |

Key: 0 = no infection, *i.e.*, neutralization; + = infection (with the incubation period).

\* Fairbrother and Brown, Lancet 2: 896, 1930.

He showed in a study of residential school boys, over a period of 6 years, that the increase in immunity was not continuous, but developed in two steps, each of which was coincident with an outbreak of diphtheria.

Kramer and Aycock (K 24) in a somewhat similar series, report a different result. They ran a series of neutralization tests upon 57 normal school children, and 20 children suspected of having passed

through abortive attacks of poliomyelitis. In October, 1930, 5 frank cases of poliomyelitis occurred in the town of Bedford, Massachusetts (population 1700), some 20 miles from Boston. A house to house canvas revealed 50 mild illnesses which might have been abortive poliomyelitis. Neutralization tests were done on 20 of these children, on 28 Bedford children who had not been ill, and on 29 children in the neighboring town of Burlington in which no poliomyelitis had been reported. The results are given in Table 78.

No appreciable difference is seen in these three groups of children, normal children from a locality in which no poliomyelitis had been reported, and normal children, both those who had and those who had not passed through a minor illness during a time when poliomyelitis was present in their locality. The authors interpret these tests as indicating

TABLE 78  
NEUTRALIZATION TEST FOR IMMUNITY TO POLIOMYELITIS, CHILDREN 5 TO 15 YEARS\*

|                                 | TOTAL | NEUTRALIZED |          | FAILED TO NEUTRALIZE |          |
|---------------------------------|-------|-------------|----------|----------------------|----------|
|                                 |       | Number      | Per cent | Number               | Per cent |
| Burlington.....                 | 29    | 13          | 44.8     | 16                   | 55.2     |
| Bedford—no illness.....         | 28    | 13          | 46.4     | 15                   | 53.6     |
| Bedford—suspected abortive..... | 20    | 8           | 40.0     | 12                   | 60.0     |

\* Kramer and Ayccock, Proc. Soc. Exper. Biol. and Med. 29: 98-99, 1931.

that immunization of a population does not take place entirely at the time of an outbreak but rather in a more or less uniform manner throughout the year, or throughout inter-epidemic periods, although this rate may, of course, vary with variations in the presence of the virus in a community. As said above, this is contrary to Dudley's conclusion as regards diphtheria, and to the results of the very small series of Fairbrother and Brown in poliomyelitis.

Weyer, Park and Banzhaf (1931, W 17) found that of 9 adults, 6 showed some neutralizing power, although in a 1:10 dilution only 4 neutralized a 5 per cent virus. Pooled convalescent serum neutralized their virus in a dilution of 1:20, but failed to neutralize in a 1:30 dilution.

Schultz and Gebhardt (1931, S 14) report tests on a total of 32 normal adults. Two techniques were used: (1) the serum and virus were incubated together for 2 hours at 37° before injection; (2) the serum-



virus mixture was not incubated. The marked difference obtained in presumably similar series of adults emphasizes the need for a standard technique if the results of different workers are to be compared. Technique (1): Of 13 normal adults, aged 16 to 48, 9 (69 per cent) neutralized in a serum dilution of 1:2. Of these 9, 2 were retested in a 1:30 dilution, neither neutralizing. Technique (2): Of 19 normal adults, aged 20 to 52 years, 9 (48 per cent) neutralized in a serum dilution of 1:2. Of the 9 which inactivated the virus, 5 were retested in a 1:30 dilution. Of these 5, 3 neutralized. These 3 were retested in a 1:60 dilution and all neutralized in that dilution as well.

The authors ran 4 human convalescent sera as auxiliaries to this series. They do not state whether or not the serum-virus mixture was incubated. Of these, 2 neutralized in a 1:2 dilution, and 2 did not. The 2 which neutralized were retested in a 1:30 dilution, neither neutralizing.

Brodie (1932, B 31) tested the sera of 29 normal adults, 13 of whom had been in continuous contact with poliomyelitis, and 16 of whom had no record of exposure. He compared the titer of these with the average of that of pooled convalescent serum:

Seven were below  $2/5$  of the average strength of the pooled convalescent sera,

Three were  $2/5$  strength,

Four were  $3/5$  strength,

Fifteen were  $4/5$  or over strength.

The tests were incomplete, but it seemed that a large proportion of the 15 would be at least equal in strength to the average convalescent serum. It was noteworthy that 62 per cent of the donors who had been in contact with the disease were represented in these 15 sera.

In another section (*Other Factors Influencing Host Resistance*), we have reported the work of Jungeblut and Smith (J 27) upon the incidence of the various blood groups in poliomyelitic patients. The characteristic change seemed to be a diminution of members of the B group in persons over 5 years, and a compensatory increase in the other groups. Jungeblut (unpublished paper read before the American Association of Immunologists, 1932) has also reported a series of neutralization tests upon normal sera, correlated to blood groups.

He tested 30 normal sera, medical students and laboratory workers aged between 22 and 35 years, all resident in New York City, many of them for a long time. These were divided equally between the blood groups O, A, and B. The results were:

| <i>Group</i> | <i>Number of<br/>Samples</i> | <i>Number<br/>Neutralizing</i> |
|--------------|------------------------------|--------------------------------|
| O            | 10                           | 6                              |
| A            | 10                           | 3                              |
| B            | 10                           | 8                              |

The author also titrated the pooled serum of each of the three groups:

| <i>Group</i> | <i>Dilution<br/>Neutralizing</i> |
|--------------|----------------------------------|
| O            | 1:20                             |
| A            | 1:5                              |
| B            | 1:60                             |

It will be thus seen that members of blood group B furnished fewer cases in persons over 5 years (Table 74); a greater per cent of normal persons of this group neutralized than of other groups; and the pooled sera of this group neutralized in a higher dilution than that of the other groups.

The authors tested also, 10 sera from pregnant women. The ages ranged from 20 to 35 years, and the stage of pregnancy varied from the third to the seventh month. Five were of the blood group A, 5 were of the blood group O. All neutralized.

Four normal women, medical students, were also tested for neutralization before and after the menstrual period. In two instances there was no difference, one neutralizing both times, one failing to neutralize both times. In one instance the serum neutralized before but not after the period, in one instance after but not before the period. Thus, while the authors regard their results as indicative of some periodic variation in neutralization as regards the menstrual cycle, they do not see a definite relationship.

*Placental Transmission of Neutralization Bodies.* That specific antibodies are placentally transmitted from mothers to their infants is indicated by a series of tests reported by Aycock and Kramer (A 45). They tested for neutralizing substances the sera of 12 urban mothers, and sera from the cord blood of their new-born infants. The sera of 9 mothers and their babies completely neutralized the virus; that of 2 mothers and their babies failed to do so. In the twelfth instance the serum of the baby neutralized the virus, while that of the mother partially neutralized.

*Neutralization Tests where Clinical Poliomyelitis is Rare.* Several authors have reported tests upon the sera of normal persons from localities where clinical poliomyelitis is rare. Aycock and Kramer (A 47) reported a series of tests upon 21 individuals who had always



lived in Atlanta, Georgia, and of whom none gave a history of clinical poliomyelitis. Reference to Table 11 will show that the morbidity rate for poliomyelitis was lower in Georgia than in any other state for the years 1915 to 1929. These individuals were all adults, all urban, and are taken, therefore, to represent the "end point" of immunization for a southern population. Of the 21 sera, 18 (86 per cent) clearly neutralized the virus, 2 failed to neutralize, 1 apparently partially neutralized. These tests indicate that immunity to poliomyelitis among adults as measured by the neutralization test, exists to the same extent in a southern city as in a northern. The authors interpret this as supporting the theory that the virus of poliomyelitis attains an equally extensive distribution in warm and cool climates, despite the greater frequency of the disease in cool regions.

These results upon the sera of southern persons have been confirmed by Hudson and Litterer (personal communication). They examined the sera of 25 normal adults of Nashville, Tennessee, and found that 21 (84 per cent) neutralized the virus when the serum was undiluted. These 21 specimens were retested in a dilution of 1:5, 16 of them neutralizing.

Soule and McKinley (S 50) report that they tested the sera of 8 normal adult Porto Ricans, all of which neutralized. Poliomyelitis is a rare disease in Porto Rico; it is not, however, unknown. Morales (M 44) reported a small epidemic of 10 cases which occurred at Vega Baja, Porto Rico, in 1928. He states in his report the opinion that the disease was not introduced from the outside but was endemic on the island.

Jungeblut (J 20b) tested sera from two places where the disease is so rare as to raise the question as to whether the persons so tested could logically be supposed to have been exposed to the virus. He tested sera from 3 Eskimos, normal adults, living on Robertson Bay, Greenland. All 3 neutralized the virus of poliomyelitis; all were of the blood group O. These sera were among those reported upon by Heinebecker and Irvine-Jones (H 17) for diphtheria antitoxin. Two of them contained antitoxin, one did not.

The above author also tested 10 sera of normal adult Chinese, all residents of Peiping, some for a long while, others for as little as a year. At the time this is written, 6 have neutralized, and 4 tests are not yet complete. These sera are among those reported by Sawyer and Hughes (paper read before American Epidemiological Society, April 8, 1932) as devoid of the power to neutralize the virus of yellow fever.

Hudson and Lennette (paper to be given before the Epidemiological Section of the American Public Health Association, October 24, 1932) have obtained similar results in the case of Liberian negroes. They examined the sera of 20 Liberian natives working inland on the Firestone rubber plantations. Eighteen (90 per cent) neutralized the virus, and one did not. One test animal died of an intercurrent infection. They used the serum undiluted. An inquiry into the occurrence of the disease led to no satisfactory information so far as Liberia is concerned. Cases in natives are reported from neighboring West African colonies, and it is possible that the same may be true of Liberia.

### PART III. MODE OF TRANSMISSION

**Infectiousness.** The infectiousness of poliomyelitis was early proposed. Schreiber (S 11) says that Landouzy first suggested in 1880 that myelopathies were infectious and that Seeligmüller (S 27) made the suggestion in the same year. Both argued from their clinical observations, Seeligmüller calling especial attention to the similarity of onset of poliomyelitis and that of other acute infections. Strümpell, in 1884 (S 66), and Pierre Marie, in 1885 (M 16), were likewise persuaded of its infectious nature, basing their opinions on their clinical observations.

It was, however, the report made by Medin (M 32) in 1890 to the Tenth International Medical Congress in Berlin upon an epidemic of 44 cases which had occurred in Stockholm in 1887, that led to general acceptance, upon epidemiological grounds, of poliomyelitis as an infectious disease.

Nearly 20 years passed before experimental corroboration of this infectiousness was obtained. Landsteiner and Popper (L 10), in 1908, transmitted the disease from a human being to 2 monkeys. Their results were soon confirmed by Knoepfelmacher (K 18). A few months later, three independent groups of workers carried the disease serially in monkeys. The reports of Flexner and Lewis in New York (F 39), of Leiner and von Wiesner in Vienna (L 27), and of Landsteiner and Levaditi in Paris (L 5) appeared almost simultaneously. With the finding of a susceptible animal, and a suitable experimental method thus afforded, observations on the etiology and immunology of the disease accumulated rapidly.

**Mode of Transmission.** Although the infectiousness of poliomyelitis was early conceded, the means by which the infective agent is transmitted was not so soon settled. Nor is there, even at the present time, unanimity of opinion. In this Section, the following possibilities are discussed:



Direct transfer from person to person, usually through droplet infection, which is the most widely accepted theory at the present time.

Transmission by milk, a mode which many believe has been demonstrated in a few instances, but which is considered to be an exceptional occurrence, and probably only accessory to contagion.

Transmission by water, a theory which is attracting much attention in continental Europe at the present time, but which is not accepted in America.

Transmission by fomites, which may, although rarely, convey infection.

Insect transmission, a theory which has been definitely rejected by most epidemiologists.

#### CONTAGION

Briefly stated, the most widely accepted theory as to the transmission of poliomyelitis is: that the etiologic agent is a filterable, ultravisible virus; that this virus is carried and disseminated only by man; that in the infective stages, the virus is present in the nasopharyngeal secretions; that it is conveyed from the sick to the well by these secretions, primarily through infective droplets sprayed about in talking, breathing, coughing, etc., though any contact between persons sufficiently intimate for the transfer to be effected will suffice.

**Experimental Evidence—Reservoir of Virus.** The virus of poliomyelitis has never been detected apart from naturally infected human beings, or from animals or articles experimentally infected. This is contrary to what might be expected when we consider the resistance under experimental conditions of the virus to such external influences as drying, cold, etc. (see *Properties of the Virus*). This failure has, however, been somewhat discounted in view of the fact that our test for the presence of virus is in monkeys, and they are naturally insusceptible to poliomyelitis, so that a relatively large dose is necessary to infect them. The fact remains, however, that so far as our present knowledge goes, the reservoir of infection is invariably human, and the virus of poliomyelitis must be classed as an obligatory parasite upon man.

If, then, the only sources of infection are human, the question arises as to where the virus is harbored by man, where it multiplies, by what route it is discharged from him, and by what medium others are infected by him. These subjects have been fully discussed under *Etiology*, and are only summarized here.

The nasopharynx is, it is believed, the site by which the virus both

enters and leaves the body. Only one other route, the gastro-intestinal, is seriously considered. The experimental data from which the conclusion has been reached consist of:

(1) The detection of the virus in the nasopharyngeal mucosa of human cases at autopsy, and in the nasopharyngeal washings of cases and contacts. (See under *Distribution of the Virus*, and under *Carriers*.)

(2) The detection of the virus in the nasopharyngeal washings of monkeys with the experimental disease. Regardless of the route by which monkeys have been inoculated, the virus can be recovered from washings of their upper respiratory passages. (See under *Distribution of the Virus*.)

(3) The production of the disease in monkeys by the nasal route, the virus having been demonstrated to pass the uninjured mucous membrane. (See under *Routes of Inoculation* and *Portal of Entry*.)

This experimental evidence for transmission by secretions of the nasopharynx is strengthened by the predominantly negative results which have been reported on experimental transmission by other natural routes. These also have been fully considered under *Routes of Inoculation*.

It is, however, a fact that natural contagion from monkey to monkey has never been noted, although well monkeys have been caged with poliomyelitic monkeys at all stages of the disease, and although the virus has been demonstrated in the nasopharyngeal secretions. This fact has been discounted on the grounds that monkeys enjoy a relative resistance to poliomyelitis, which is broken down only with difficulty; but on the other hand, it is also true that no instance has ever been recorded where a worker in a laboratory whose duty was to handle infected monkeys, has been infected. Levaditi and Danulesco (L 38) did report that a monkey, which had been kept for 18 days in a cage the bars of which were smeared with virus, developed the disease on the twentieth day from the first contact with the virus, but this result has not been confirmed.

**Epidemiological Evidence.** As early as 1888, Cordier (C 26) observed 13 cases of poliomyelitis at Ste.-Foy-l'Argentiere and was convinced that the disease was contagious—so convinced that he advised the removal of very young children from epidemic areas. Later, Wickman gave great emphasis and considerable evidence as to this mode of spread. He was able to trace very complete lines of contact between cases, either directly or through intermediaries. (See under *Direct Contact*, and *Carriers*.)



Later epidemiologists have not, however, found the evidence as to the contagiousness of poliomyelitis so clear-cut and conclusive, as that reported by Wickman. Certainly poliomyelitis, as we ordinarily encounter it in the United States, does not behave epidemiologically in accordance with the concepts that have become crystallized as to how a contagious disease should behave. Greenwood (G 17), in a recent paper says, "An illness is held to be 'catching' when it has usually been possible to explain the existence of a case of it by close association with an immediately preexisting case; the notion of more or less infectiousness depends on some appraisal of the proportion of persons attacked to persons exposed to the risk of attack." Judged by either criterion, *i.e.*, by demonstrable contact between cases (see under *Contact Traced*) or by increased incidence among those exposed to the sick (see under *Multiple Cases*), the contagiousness of poliomyelitis is slight, even debatable.

It is true that the negative epidemiological as well as the negative experimental evidence as to any other mode of spread has perhaps unduly influenced the acceptance of the theory of direct transfer of the virus from person to person, following Chapin's (*Sources and Modes of Infection*, 1912) dictum that since contagion is the simplest mode of spread, the burden of proof lies in disproving it.

### The Theory of Latent Immunization

These apparent discrepancies in the arguments for the contagiousness of poliomyelitis, the failure to demonstrate contact between cases and the lack of increased incidence among those known to have been exposed, have been met by the theory of latent immunization.

The theory of widespread latent immunization or latent epidemisation predicates, as regards poliomyelitis (1) that innate resistance of individuals to the disease is high; (2) that infection and disease are not identical, but that exposure to the virus results, in a large majority of cases in an immunity response, and only exceptionally in the clinical disease, and then frequently without involvement of the central nervous system; (3) that the virus is extensively spread, infection being common and frequent; (4) that the differences in the epidemiology of poliomyelitis and the more common droplet contagions are due not to a difference in the mode of transmission, nor to a difference in the extent to which the etiologic agents are disseminated, but to an increased ratio of sub-clinical to clinical infections in the case of poliomyelitis.

(1) It is evident that the innate resistance of individuals to polio-

myelitis must be high. As Friedemann (F 68) says, "In an extensive epidemisation we may assume two factors, a very small inborn susceptibility of individuals to the contagious disease, and an extensive spread of the specific microbes. The first statement does not need any interpretation. If the microbe is so virulent for man that infection coincides with symptoms of the disease, we experience a manifest, not a latent, epidemisation—for example measles."

Great epidemiological importance is, therefore, to be attached to the nonspecific resistance which individuals possess toward the virus of poliomyelitis, since in any infection, the significance of the resistance factor varies with the ratio of subclinical to clinical infections.

(2) This theory emphasizes that infection and disease are not identical. Halliday (H 4) has summarized the various possibilities that may follow infection:

"(a) The virus may not succeed in implanting itself on the respiratory passages and may die out.

"(b) The virus may begin to multiply in the respiratory passages, thus provoking the individual to react. It may happen that a bodily reaction accompanied by no obvious clinical disturbance may be sufficient to check the activity of the virus, and the individual will gain what is called a 'subclinical immunity.' If the reaction should be more severe, clinical disturbance will be manifest, resulting in the individual being recognized as a 'case' either of abortive or of fully developed poliomyelitis.

"(c) A symbiosis of virus and individual may be maintained for varying periods of time, healthy persons as well as 'cases' becoming *carriers* of infection."

In the latter two of these events, the individual is presumably able to infect others.

We must, therefore, differentiate between infection followed by disease and infection without disease. The latter constitutes the subclinical infections or subinfections. Kling and Levaditi (K 12) during the Swedish epidemic of 1912 found that the sera of normal contacts neutralized the virus, and stated the opinion that this immunity was due to latent infections, the organism reacting to the virus only by the production of antibodies. This is, so far as we are aware, the first suggestion of the development of immunity in response to subinfective doses to be made in connection with poliomyelitis, although the idea was by no means new in connection with other diseases.



### Primary Exposures.

If infection and disease are not identical, what factors determine which of the above possibilities will be the outcome of initial infection? Why does the exceptional person, estimated by Aycock to be less than 1 per cent of those infected, develop poliomyelitis, while the 99 develop a specific immunity? The most important factor unquestionably lies in the constitutional makeup of the persons themselves, in some deviation from the normal which renders them more susceptible. The various ways in which persons may so vary is considered under *The Epidemiology of the Host*.

Other factors which may influence the outcome of initial infection are:

*Dosage.* Dudley's theory (D 27; D 28) of "Velocity of Infection" states this factor thus: In many or all infectious diseases, a certain mass of infective agent, a certain minimal infective dose, is necessary to produce an illness. This mass may be received at various rates by an individual who can destroy the infective agent at a certain rate. The difference between these rates may be positive or negative. If positive, illness will supervene, provided that the subject of infection stops long enough in the same relation to the source of infection. The greater this positive difference, the less time will be required in the infectious environment in order to produce a case or a carrier. The difference between the rate of reception and destruction of microbes is termed the "velocity of infection." If this velocity is negative no actual illness occurs, but the defense mechanism of a recipient host may be stimulated and increased so that if subsequently exposed to a much greater velocity of infection, or massive single doses of the microbic parasite, he suffers no ill result—he has been vaccinated against the infective organism.

This theory, it will be seen, emphasizes the part played by time in the production of infection. Dudley believes that it is more often than not the rule for an infectious dose to be collected by degrees rather than as a whole in one moment of time.

This idea of cumulative doses receives support in the case of poliomyelitis from the results in the experimental disease, in which it is possible to infect monkeys by reinoculation with strains which otherwise are ineffective. (See *Routes of Inoculation*.)

*Virulence.* In as much as strains of poliomyelitic virus have been demonstrated to vary for monkeys both in infectivity and in virulence (see under *Properties of the Virus*), it seems only reasonable to suppose that strains also vary for humans, although not necessarily the same strains.

The question of strains is considered under *Etiology*.

*Season.* The possibility exists that infection with the virus may cause the clinical disease, or immunity, depending upon the season of year. This may be due to seasonal variation in the infectivity or virulence of the virus, or to seasonal variation in the resistance of the host.

**Secondary Exposures.** The result of secondary exposures to the virus will depend on these factors enumerated above plus one additional factor, the amount of specific immunity developed in response to the primary infection. If the primary infection resulted in disease, this immunity will be almost absolute, there being very few instances of second attacks of the disease. If the primary infection initiated an immunity response, there will be this added protective mechanism.

It is therefore seen that there are two factors limiting the incidence of the disease—the host resistance and the specific immunity. Since the specific immunity is believed to be a factor only when infection has occurred and been either overcome owing to the nonspecific factor, or resulted in the disease, it will be seen that the nonspecific resistance is of importance in limiting the disease in both primary and secondary infections, while specific immunity limits the disease only in secondary infections.

(3) The theory of latent epidemisation predicates also that the virus of poliomyelitis is widespread. The theory is, therefore, conditional upon the assumption of a large number of unrecognized cases and healthy carriers who constitute at once the reservoir of the virus, and the invisible links between seemingly unconnected and isolated cases. As stated in the *Section on Carriers*, the assumption of such numbers of healthy carriers has not been corroborated experimentally. In only two instances has the virus been detected in persons who were not known to have shown clinical symptoms.

(4) This theory leads us to the conclusion that the various air-borne or droplet infections are alike in that their causal organisms are widespread, and infection with them common. They differ from each other however, very strikingly in the extent of host resistance; in the resulting ratio of clinical disease to infection; and therefore in the extent to which the immunization of a population will be manifest.

Against the viruses of certain diseases, measles and smallpox for example, there appears to be no resistance, infection and disease being equivalent, immunity resulting only from the disease and being, therefore, clearly manifest. Poliomyelitis represents the other extreme: innate resistance is high; infection results only exceptionally in the clinical



disease; immunity may follow either subclinical or clinical infections; to the extent to which the former exceed the latter, to that extent will the latent exceed the manifest epidemisation.

**Arguments for and against Latent Immunization.** The chief arguments advanced in favor of latent immunization have been (1) the neutralization tests upon normal persons, (2) the age incidence, (3) analogy to the bacterial diseases in which more definite proof has been offered.

(1) *Neutralization Tests upon Normal Persons.* The results which various workers have obtained in neutralization of the virus of poliomyelitis by the serum of persons who have not been known to suffer from the disease have been considered under *The Epidemiology of the Host*. It has not been possible to do these tests upon a large number of people, since at present a test for neutralization bodies in serum involves the use of one monkey for each dilution of the serum tested, which is prohibitive for very extensive series.

In spite, however, of the limited material available for analysis, no question in the epidemiology of poliomyelitis has been so widely considered as the significance to be attached to the fact that the sera of a large percentage of normal persons tested neutralizes the virus. Such neutralization has until recently been regarded as conclusive evidence of a specific response to previous subinfective doses of the virus. The earlier neutralization tests reported were corroborative of this opinion: the percentage of persons whose sera neutralized the virus increased with age; at corresponding ages, more persons in urban communities neutralized than in rural communities. That is, neutralization seemed to increase with increased probability of exposure.

Recently, however, there have been accumulating certain puzzling and paradoxical results as to neutralization. In the *Section on Neutralization Tests on the Sera of Normal Persons*, we have given the results obtained by various workers on neutralization of poliomyelitic virus by the sera of persons living in places where the clinical disease is rare, or even where it has questionably been observed. These results are reviewed in detail in that section, but may be briefly summarized here:

| Author              | Residence of Persons Tested | Number Tested | Number Neutralizing | Per cent Neutralizing |
|---------------------|-----------------------------|---------------|---------------------|-----------------------|
| Aycock              | Atlanta, Georgia            | 21            | 18                  | 86                    |
| Hudson and Litterer | Nashville, Tenn.            | 25            | 21                  | 84                    |
| Soule and McKinley  | Porto Rico                  | 8             | 8                   | 100                   |
| Jungeblut           | Eskimos, Greenland          | 3             | 3                   | 100                   |
| Hudson and Lennette | Liberian Negroes            | 20            | 18                  | 90                    |

We may profitably compare these results with those obtained with the sera of persons residing where poliomyelitis is most common:

| <i>Author</i>            | <i>Residence of Persons Tested</i>    | <i>Number Tested</i> | <i>Number Neutralizing</i> | <i>Per cent Neutralizing</i> |
|--------------------------|---------------------------------------|----------------------|----------------------------|------------------------------|
| Aycock and Kramer        | Boston, Mass.                         | 8                    | 7                          | 87.5                         |
| Ibid.                    | Rural New England                     | 5                    | 2                          | 40                           |
| Shaughnessy, et al.      | Chicago, rural Illinois, and Winnepeg | 9                    | 8                          | 88.8                         |
| Weyer, Park, and Banzhaf | New York City                         | 9                    | 6                          | 66.6                         |
| Schultz and Gebhardt     | San Francisco                         | 32                   | 18                         | 56.2                         |
| Jungeblut                | New York City                         | 30                   | 17                         | 56.6                         |

These two sets of results, one from localities where the disease is commonest and the other from localities where the disease is rarest, emphasize the fact that the power of neutralization proceeds at a rate independent of the incidence of the clinical disease. Two possible explanations present themselves, (1) localities may vary markedly in the incidence of clinical cases, but the incidence of infections may be as high or higher in localities with a low disease rate as in those with a high, that is, localities may differ, not in the number of infections but in the percentage of these infections which result in disease, or (2) neutralization may not be proportional to opportunity for exposure.

The recent results reported by Kramer and Aycock (K 24), which were referred to in the *Section on Neutralization Tests*, may be interpreted as corroborative of the latter view. These authors state that the small town of Bedford suffered, in 1930, a relatively severe outbreak of poliomyelitis (5 cases in a total population of 1700, a morbidity rate of 2.9 per 1000). Five months later they tested 20 Bedford children who had passed through minor illnesses at the time of the outbreak, and 28 Bedford children who had remained well. As a comparison they tested 29 children of similar ages in the neighboring town of Burlington in which no poliomyelitis had been reported. The results are given in Table 77. No appreciable difference was found in these three groups.

An editorial in the *Journal of the American Medical Association*, 1932 (E 8), comments that "since Wickman first assumed the existence of an abortive form of poliomyelitis, the impression has become general that much, if not all, of the adult immunity to this infection is due to mass immunization of growing children by unrecognized subclinical attacks of the disease. Doubt as to the validity of this conclusion is implied in the current epidemiological studies of Drs. Kramer and Aycock. While



the Harvard investigators have not yet abandoned the conventional assumption that adult resistance to poliomyelitis is due to childhood contact with the specific virus, they seem to have been forced to the conclusion that effective contact with the immunizing virus does not take place at the time of epidemics. Apparently the immunization is a more or less continuous process extending throughout the year, or perhaps even limited to interepidemic periods. Their data, however, are equally consistent with the recent radical European theory that the adult immunity is not so much due to specific contact with the infecting agent as to a nonspecific 'serologic ripening' or 'physiologic maturation' roughly synchronous with the development of sexual maturity."

Another editorial in a later issue of the *Journal of the American Medical Association*, 1932 (E 9), concludes: "There is increasing difficulty in harmonizing the known facts of the epidemiology of poliomyelitis with the historic belief that adult immunity to this disease is specific and can result only from previous personal contact with the virus."

(2) *Age Incidence.* A further argument in favor of subclinical infections and a consequent latent immunization has been that the age incidence of poliomyelitis places it among the "diseases of childhood," and that the progressive integration of specific immunity through a population can explain much, if not all, of the freedom from the disease enjoyed by the older age groups.

Under *The Epidemiology of the Host, Age Incidence*, we have given the figures which show that the age incidence of poliomyelitis varies inversely with the density of population, being lower in more densely, higher in more sparsely settled communities. The theory of latent immunization explains this by assuming that in densely populated communities, which are in frequent communication with other communities, a continuous reservoir of infection is maintained. In more dispersed and isolated populations, the virus is less constantly present, being probably introduced from time to time, but not maintaining itself continually. Immunization proceeds more rapidly and more regularly in the former, more slowly and more variably in the latter. The rate of immunization, therefore, which depends upon the rate of spread of the virus through a population, appears then to be governed by the general principles of mass action, the more concentrated the population the faster is immunization accomplished, the younger will be the average age of the susceptible population, and the earlier the age incidence of the clinical disease.

Neufeld (N 10), although he accepts the theory of latest immuniza-

tion, *i.e.*, a widespread virus with many subclinical infections resulting in a specific immunity, thinks the theory is not an inevitable conclusion from the age distribution of poliomyelitis. He points out that the low incidence of the disease may be explained on the basis of a high natural resistance—a limited number of susceptibles, and the increased involvement of early childhood in urban populations on the basis of higher exposure with increasingly denser population, and an earlier exhaustion of susceptibles.

In the age incidence, as in the neutralization tests, we meet the paradox of the age incidence being lowest where the clinical disease is least prevalent. This relation of latitude to the age incidence is discussed under *Age Incidence*.

(3) *Analogy with Certain Bacterial Diseases*. In certain of the bacterial diseases, diphtheria and meningococcic meningitis for example, it has been possible to establish a carrier rate sufficiently high to justify the assumption that the immunity enjoyed by the older age groups is largely a result of exposure. Undoubtedly the strongest argument for latent immunization in poliomyelitis is an analogy to these diseases where the evidence is stronger. It becomes necessary to carry the assumption farthest in explaining the ratio of subclinical to clinical infections in the case of poliomyelitis where there is least to substantiate it.

**Objections to Latent Immunization from Experimental Viewpoint.** The objections from the experimental point of view which have been raised to the theory of latent immunization have been summarized by Jungeblut and Engle, 1932 (Paper read before the American Medical Association, Section on Nervous and Mental Diseases, May, 1932) thus:

(a) The specific origin of so-called natural antibodies can no longer be unreservedly accepted. This is further considered in the following section, *The Theory of Maturation*.

(b) Strains of normal invasiveness but low virulence have not been demonstrated.

Flexner and Amoss in 1924 (F 30) reported a single exception, a strain which, while possessing normal invasive power, showed a low degree of virulence for monkeys, with marked protective power. It is interesting to note that this strain was derived from a human case of unusual clinical severity, with exceptionally intense histological lesions. The significance of this fact was, however, somewhat clouded by the fact that the virus-containing tissue was putrefactive on receipt and recourse was had both to glycerol and later phenol. The authors were in doubt as to



whether the attenuation was a result of putrefaction, or an inherent property of the strain.

Strains which cannot be implanted upon monkeys, *i.e.*, of low invasive power for monkeys, are, of course, frequently encountered, even from fatal human cases.

(c) The implied assumption that subinfective doses of the virus entering through the accepted portal, the nasopharynx, produce a high and durable immunity, has not been experimentally verified. Jungeblut and Hazen (J 24) reported negative results upon 4 *rhesus* monkeys subjected to spraying of the nose and throat with poliomyelitis virus semi-weekly for  $2\frac{1}{2}$  months. The sera of the 3 surviving monkeys did not neutralize the virus, and the monkeys were not immune to subsequent intracerebral inoculation.

(d) Active experimental immunization against poliomyelitis by any method has been of low efficiency even when large doses of virus are employed.

They conclude, "The extent of the natural resistance to poliomyelitis observed in human populations seems utterly disproportionate to the quantities of virus which would seem to be postulated by analogy with these experimental results."

### The Theory of Maturation

Resistance to poliomyelitis certainly increases with age. A part of this resistance is almost undoubtedly due to a specific immunity caused by infection with the virus. A part is, probably, though less certainly, due to a resistance which increases with age, which is inherent in maturity, and which is not due to exposure.

There are two viewpoints to such a maturation theory: that there is a clearly nonspecific resistance which increases with age, and that there are antibodies which develop with age, which may or may not be identical with the antibodies developed as a result of infection, but between which no differentiation has as yet been possible.

**Nonspecific Resistance.** A nonspecific resistance that increases with age has been definitely demonstrated in the case of diphtheria. Doull (D 17) has shown that immunity as measured by the Schick test does not fully account for the lower attack rate among adolescents and adults. Resistance by Schick-positive persons must also increase in frequency with age, since the estimated attack rates for Schick-positive individuals in family contact with diphtheria decreases with age. In his article Doull gives a chart which he made from the figures of Chapin for Providence and which shows this plainly.

While the evidence in poliomyelitis is not extensive, it is suggestive. The attack rates during the 1916 epidemic in New York City, when presumably the virus was widespread, are given in Table 79, and the results of Aycock and Kramer (A 46) of neutralization tests upon urban individuals at different ages in Table 80. By comparison with other urban sera (see under *Neutralization Tests upon Normal Individuals*), the figures of Aycock and Kramer give a high percentage of adult sera which neutralize, *i.e.*, the range is wider than in most series.

TABLE 79  
ATTACK RATES AT DIFFERENT AGES, NEW YORK CITY, 1916\*

| AGE                 | CASES PER 100,000 PERSONS |
|---------------------|---------------------------|
| 0 to 4 years.....   | 1,339                     |
| 5 to 9 years.....   | 316                       |
| 10 to 14 years..... | 49.7                      |
| 15 to 19 years..... | 16.1                      |
| 20+ years.....      | 3.6                       |

\* Lavinder, Freeman and Frost, Public Health Bull. 91, 1918.

TABLE 80  
NEUTRALIZATION TESTS UPON NORMAL URBAN SERUMS, BY AGE GROUPS\*

| AGE                 | URBAN, NUMBER | PER CENT IMMUNE | PER CENT NON-IMMUNE |
|---------------------|---------------|-----------------|---------------------|
| 0 to 4 years.....   | 12            | 41.7            | 58.3                |
| 5 to 9 years.....   | 10            | 80.0            | 20.0                |
| 10 to 14 years..... | 9             | 66.7            | 33.3                |
| 15 to 19 years..... | 7             | 85.7            | 14.3                |
| Adult.....          | 8             | 87.5            | 12.5                |

\* Aycock and Kramer, J. Prev. Med. 4: 196, 1930.

The results of Aycock and Kramer in testing the power to neutralize the virus possessed by normal urban people, most of them living in or near Boston, however, show no such variation as to age as is seen in the attack rates. Thus we see that the attack rate in New York City in children under 5 was 372 times as great as in persons 20 years of age or over. In the series of Aycock and Kramer, however, the sera of urban children under 5 failed to neutralize about 5 times as often as that of adults.

It is not to be implied, certainly, that a curve of age incidence of



immunity or non-immunity should correspond to that of age incidence of the disease. The latter is compounded of both the former and the added factor of exposure. It would seem, however, that exposure in the older ages should be as great, if not greater than in the lower.

It must be said, of course, that the series of neutralization tests is small, and the communities not strictly comparable. The magnitude of the difference in attack rates, and demonstrable antibodies by neutralization tests is, however, very great.

**Development of Antibodies with Age.** There is also the theory which holds that defensive antibodies, possibly nonspecific, are formed and increased as part of a general serological ripening, roughly synchronous with the development of sexual maturity. This theory questions the traditional belief that specific antibodies are due entirely to reaction to infection and regards this additional method as the expression of an endogenous hereditarily fixed maturation process which reaches its climax around puberty.

Observed mass immunization to poliomyelitis, and certain other transmissible diseases, is not, then, according to this theory, in all cases necessarily due to previous subclinical infections. The work of Friedberger, Bock and Fürstenheim (F 66) is cited as showing that certain antibodies, hemolysins and hemagglutins, can be formed without antigenic stimulation. Friedberger and Heim (F 67) have also argued for a similar development of immunity in the case of diphtheria.

**Experimental Data.** There is very little evidence available as to the influence of age on susceptibility in experimental poliomyelitis. Leiner and von Wiesner (L 28, I; Z 3) found that the age of the animals employed affected in some measure the success of infection. Their negative inoculations were for the most part those in which large powerful animals had been used. Levaditi (L 34) says that young monkeys are more receptive than old simians. There seems to be a general assumption in the literature that this is true, although sufficient definite proof is lacking. This is doubtless due to the fact that old monkeys are difficult to obtain, and young monkeys are difficult to rear in captivity, with the result that nearly all the reported work has been done on young monkeys.

The sera from young monkeys have been uniformly reported as devoid of the power to neutralize the virus of poliomyelitis *in vitro*. Jungeblut and Engle (J 21), however, found that 2 samples out of 12, taken from normal adult *rhesus* monkeys, neutralized. Their results also indicate that there may be a relationship between neutralization

and the menstrual cycle, since the sera from the 2 animals which neutralized were taken after the cycle, and sera from the same monkeys failed to neutralize during the cycle. They say, "Our experiments suggest that the protection enjoyed by adult humans is due not so much to latent immunization by contact with the virus as was formerly believed, but rests primarily on the hormonal balance characteristic of adult life."

Jungeblut and Engle (J 22) have found also that feeble virucidal substances may be found in the blood of monkeys after an artificially produced change in their endocrine balance. They also obtained neutralizing effect with certain samples of serum from other animals which are normally insusceptible to the disease, such as sera from horses, sheep, and *cebus* monkeys.

These authors do not attempt at present to say whether or not this alexin-like normal neutralizing factor is identical with the typical immune body resulting from recovery or produced by specific active immunization. The subject has been dealt with under *Immunity*.

**Cross Protection of Infectious Diseases.** The possibility that immunity to one infectious disease may develop from contact with the etiologic agent of another disease is also suggested by the *Journal of the American Medical Association* (E 9), which quotes the work of Heidelberger, Goebel, and Avery (H 16) who showed that the characteristic antigenic sugar of type II pneumococcus is also found in the Friedländer bacillus. Similar chemical relationships have been shown to exist in other organisms. Recently, Zozaya (Z 10) showed that a sugar of at least approximately the same antigenic potential as the characteristic polysaccharide of the meningococcus is demonstrated in *B. anthracis*, and, even more surprising, is present in such common saprophytes as *B. proteus*, *B. subtilis*, and *B. mesentericus*.

That such cross protection may have a bearing upon immunity to poliomyelitis is also suggested by the results of Zingher in Schick-testing children suffering from poliomyelitis.

*Reaction of Poliomyelitic Children to the Schick Test.* During the poliomyelitis epidemic of 1916 in New York City, Zingher (Z 6) tested by the Schick reaction 1350 children admitted to the Willard Parker Hospital. Of the 954 city children between 1 and 4 years of age, 774 (81 per cent) were Schick-positive. In his control series in normal city children of the same age group, positive Schicks varied 30 to 40 per cent. (This is the usual percentage. Park reports 60 per cent Schick-negatives in the similar age group.) In measles a slightly higher



proportion of cases were Schick-positive than normals, while in scarlet fever, about 68 per cent were positive. The children were retested later to eliminate the possibility that the positive reaction represented merely a temporary loss of antitoxin during the febrile stage of the disease. The reaction continued positive.

That children who have failed to develop a subclinical immunity to one contagious disease should also be susceptible to another is capable of several interpretations. First, as mentioned, the possibility of cross protection in certain infections, must be considered. It may represent an individual peculiarity or inability on the part of some children to react to subclinical doses of any of the infections. It may, on the other hand represent an abnormality of development or "serological ripening," a child who has failed to "mature" normally in regard to one disease may also lack the power to "mature" normally in regard to others. Or again, it may indicate that any group of children who have lived under an environment in which exposure to one disease has been so limited that subclinical immunity has not developed, will also have had relatively fewer exposures to the other communicable diseases. It is uncertain at present whether the peculiarity lies in the individual or his surroundings.

**Arguments against the Theory of Maturation.** Aycock (A 37) argues against the development of antibodies with increasing age without specific antigenic stimulation. His arguments that the virucidal antibody is an indication of exposure to the virus are:

"1. It is not found in an animal not known to have been exposed.

"2. Experimental immunity has been produced only by the particular disease virus.

"3. Immunity develops only under circumstances in which association with the virus is possible.

"4. The development of immunity follows laws of infection and does not follow any law of maturation. As pointed out, it does not occur when the virus is absent. In areas in which the virus is present, it varies in accordance with variations in opportunities for exposure. Thus, while in a general way, it increases with age, this varies with the concentration of population in a manner consistent with variation in opportunity for exposure and inconsistent with any law of maturation.

5. In the case of diphtheria, ample evidence is available to show that the distribution of this organism is of sufficient extent to account for the observed adult immunity to diphtheria."

He concludes that "one is led to believe that what has been called panimmunity is evidence of paninfection."

**Conclusions.** Neither theory can be regarded as proved nor disproved. There does not now seem to be anything mutually exclusive in them, and the question may be shown to be one of relative emphasis. Dr. Park has expressed the view that "the truth undoubtedly lies somewhere between these two points of view."

#### NON-HUMAN CARRIAGE

##### TRANSMISSION BY MILK, WATER, OR OTHER INGESTED MATERIAL

The possibility that the virus of poliomyelitis may be transmitted by milk or water has recently attracted considerable attention. Some outbreaks have pointed toward milk as the responsible agent, and certain European epidemiologists are expressing the opinion that there is a relation between outbreaks of poliomyelitis and water supplies.

A number of questions present themselves as relevant to the question of spread of the virus by ingested material:

1. By what route or routes may infection occur if the virus is milk-borne or water-borne?

2. Are the feces infective? This question is especially applicable to water-borne infection, since milk may become infected through the nasopharyngeal secretions.

3. Do the pathological or clinical findings of the disease point toward an alimentary infection?

4. Does the virus survive in milk? Does it survive in water?

(1) **Route of Infection.** Infection from contaminated milk, or possibly water, might be through the pharyngeal mucosa, as in milk-borne outbreaks of epidemic sore throat and diphtheria, or by the gastrointestinal tract.

(a) The evidence as to infection by the nasopharynx has been considered under *Etiology and Pathology*. It would not seem to require any different mechanism for infection to occur through the pharyngeal mucosa once the virus has attached itself, whether the virus was borne there by milk or by droplets of human secretions.

(b) Infection by the gastro-intestinal route: In so far as we can judge from attempts to produce the experimental disease, natural infection by the gastro-intestinal tract seems to be possible, though not probable. A few positive results have been reported. Leiner and von Wiesner (1910, L 28, II), Kling, Levaditi and Lépine (1929, K 13), Levaditi, Kling and Lépine (1931, L 43), and Saddington (1932, S 3) report successful inoculations by this route.

Negative results have been reported by Landsteiner and Levaditi



(1910, L 6), by Schultz (1929, S 12), by Thompson (1930, T 8), by Clark, Schindler and Roberts (1930, C 16), by Jungeblut (1932, personal communication), and by Clark, Roberts and Preston (1932, C 15).

Clark, Roberts and Preston (1932, C 15) say as to their own experiments, although the comment is equally applicable to the results of other workers: "In evaluating these experiments, one must keep in mind the fact that no animal has been found which is so susceptible to poliomyelitis as is the human being. While the disease in the *Macacus* monkeys is quite typical of the human both in lesions and clinical picture, yet no contact cases occur with these animals, even when normal monkeys are kept in closest intimacy with those acutely ill. Also, in attempting to produce poliomyelitis by feeding, one must be aware of the possibility of infection through the tonsils or even by the nasal route, through regurgitation of the virus. By the use of the stomach tube we have endeavored to avoid the nasopharynx, but even this method presents the possibility of infecting that area during the withdrawal of the tube. It may well be that the tonsils are frequently a primary site of infection both in milk-borne and droplet infection cases."

(2) **Infectiousness of Feces.** The question of the infectiousness of feces is of especial importance in evaluating Kling's theory that the virus of poliomyelitis is water-borne. Milk might also be contaminated by this means, but the possibility of infection through milk does not so hinge upon this question, since milk might also be contaminated from the nasopharyngeal secretions, but the possibility of water so infected transmitting the disease is very remote.

The virus has not been recovered from the feces of human cases.

Clark, Schindler and Roberts (C 16) report that they were unable to infect monkeys with a concentrate of feces from acute cases of experimental poliomyelitis; in 1 experiment out of 6, however, the feces, obtained following the feeding of large volumes of poliomyelitis virus, gave an inoculum with which the disease was experimentally produced. They conclude that the virus does not commonly pass through the intestinal tract of monkeys in an infective form.

Levaditi, Kling and Lépine (L 43) reported that they had recovered the virus from the feces of 1 monkey infected by mouth, 24 and 48 hours after ingestion; while on the eighth and thirteenth days, their results were negative. In other cases they found the feces to be uninfected, whether or not the animal developed the experimental disease.

Clark, Roberts and Preston (C 15) reported that, while they had not

been able to recover the virus from animals with the experimental disease, they had demonstrated it in the feces from monkeys that had been infected in various ways:

(a) from monkeys into a loop of whose small intestine virus had been injected;

(b) from monkeys that had been fed various preparations of virus-containing material for varying times.

(3) **Pathological Changes in the Gastro-intestinal Tract.** Various authors have noted lesions in the alimentary canal. These are considered under *Pathology*, and need not be considered here, except to call attention to the fact that they are suggestive of infection by this route.

Kling (K 11) argues for the disease being water-borne (although the arguments are equally applicable to milk):

(a) the prominence of intestinal symptoms among the prodromata of poliomyelitis—vomiting, constipation, diarrhea, and

(b) the more frequent affection of the legs than of the upper part of the body. Fairbrother and Hurst (F 6) have, however, refuted this latter line of reasoning by pointing out that the legs are also the site of onset of paralysis in 70 per cent of monkeys following intracerebral inoculation. Attention might also be called to the fact that MacNalty (N 10) says that in the Broadstairs epidemic of 1926 which Aycock attributed to milk, the most prominent clinical feature of the epidemic was the unusual number of cases of polio-encephalitis.

#### (4) **Survival of Virus in Milk, Butter, and Water**

(a) *Survival of Virus in Milk.* Landsteiner, Levaditi and Pastia (L 8) were able to demonstrate the survival of poliomyelitic virus in milk after 31 days.

Park (personal communication) and his co-workers at the New York City Research Laboratories, have a virus which, placed in milk and stored in a refrigerator, is still viable after 6 months. The virus has very slowly decreased in amount.

Multiplication of the virus in milk has not been demonstrated. An ability to survive, but not to proliferate on the part of the virus would necessitate very heavy seeding at the time of contamination.

Isolation of the virus from naturally contaminated milk, could not, in view of the experimental difficulties, be expected.

(b) *Survival of Virus in Butter.* Kling, Levaditi and Lépine (K 14) report a series of experiments showing that poliomyelitis virus, mixed with butter (both commercial butter and butter made by



adding 5 per cent lactic acid to cream) retained its virulence for monkeys as long as 91 days, when kept at 2°C. This occurred despite the rather pronounced acidity of the contaminated butter.

(c) *Survival of the Virus in Water.* Landsteiner, Levaditi and Pastia (L 8) reported that virus mixed with sterile water, kept at room temperature and light, survived for 25 days. The incubation period for monkeys was prolonged, however, indicating to the authors an attenuated virus. Kling, Levaditi and Lépine in 1929 (K 13) diluted a cord emulsion from a monkey with a fairly large quantity of sterile tap water; this was kept at room temperature out of the light. The emulsion was found to be infective for monkeys as late as the 114th day. There was no evidence that the virus increased in the water.

(d) *Filtration.* It is obvious that filtration of water would not be effective against poliomyelitis, since the virus itself is filterable.

(e) *Effect of Chlorination upon Virus.* Only one test of the effect of chlorination upon the virus has been reported. Because of an undetermined amount of chlorine-consuming matter, such as organic substances, the test was quantitatively indeterminate. Levaditi, Kling and Lépine (L 43) state that when the virus is present in distinctly cloudy emulsion in tap water even after filtration through paper or cotton, it is sterilized in 24 hours by the addition of 4 milligrams of chlorin per liter. One-tenth of this amount, 0.4 milligram per liter, sterilizes virulent limpid water. They concluded that under usual conditions chlorination of drinking water with normal quantities of chlorin is sufficient to render it safe from possible contamination by poliomyelitis virus.

Chlorination of water is generally considered satisfactory in the United States if a residual of 0.1 part per million (0.1 milligram per liter) remains after a contact period of 15 minutes, or 0.2 part per million after 5 minutes.

In the New York City water supply, the initial amount of chlorin added is generally less than 0.5 part per million. The dose is considered adequate if, at the dosing plant, a residual of 0.1 part per million chlorin remains after 10 minutes. In some of the well water supplies, 0.05 part per million is added. With this treatment, *B. coli* is absent in 100 cc. of treated water.

## Milk

**Relation of Cases to Source of Milk Supply.** Because poliomyelitis selects typically the age group which ingests milk, and because the great majority of cases occur in the months when milk is especially vulnerable

the milk supply was considered in a number of the early epidemics. It soon became obvious that poliomyelitis could not be solely or even primarily milk-borne. Many cases are reported among persons who have used no milk at all, or only pasteurized milk, and for babies entirely breast-fed to have the disease is a not infrequent occurrence.

The figures for the Borough of Richmond, of which a special study was made during the New York City epidemic of 1916 (L 16) are typical:

|                              | Cases |
|------------------------------|-------|
| Using cow's milk, fresh..... | 240   |
| condensed milk.....          | 12    |
| condensed and breast.....    | 1     |
| breast feeding only.....     | 8     |
| no milk of any kind.....     | 11    |
| Total.....                   | 272   |

That is, out of 272 cases, 32 used no cow's milk from any source. No information is given as to whether the 'fresh' milk was raw or pasteurized, but the sanitary code required that it be pasteurized.

In Buffalo, in the 1912 outbreak, Frost (F 71) reports that:

Out of 265 patients, 224 used more or less of *raw* milk from the following sources:

|                                              | Cases |
|----------------------------------------------|-------|
| Licensed dairies.....                        | 209   |
| Local groceries.....                         | 11    |
| Private sources (own or neighbor's cow)..... | 5     |
|                                              | 225   |

Forty persons used no raw milk at all, viz.,

|                                                 |     |
|-------------------------------------------------|-----|
| No milk at all.....                             | 4   |
| Only boiled, condensed, or evaporated milk..... | 24  |
| Exclusively breast-fed.....                     | 12  |
| Total.....                                      | 265 |

In 32 instances, the supply was not determined. The 209 patients supplied by city dairies obtained their supply from 120 different dairies, none of which supplied milk to cases out of proportion to the amount distributed. The same author, on page 157 of the same report, gives similar data for the epidemic in Cincinnati, Ohio, in 1911.

**Outbreaks Attributed to Milk.** The reports of some seven groups of cases, however, where the evidence pointing toward milk as the mode of spread is strong, would indicate that transmission by milk may play in poliomyelitis, as it does in diphtheria and scarlet fever, a rôle ac-



cessory to contact infection. Although the total number of cases which have been attributed to milk is small, the subject is, because of the potentialities, important out of proportion to the numbers involved.

This paucity of evidence may not, however, represent the actual importance of this mode of transmission, as is indicated by Godfrey (P 28), who calls attention to the fact that the almost total lack of evidence in 1911 that poliomyelitis might be spread by milk was responsible for the omission of any query concerning the milk supply from the investigation form adopted by State and Federal Health authorities in 1911, when the disease was made reportable, and that this omission may, in turn, have precluded the recognition of evidence pointing toward milk, even if there had been any. This omission becomes the more significant when we realize that milk-borne outbreaks of all diseases are becoming more and more limited to smaller supplies where sanitary control is inadequate and pasteurization is not compulsory. Thus we should not expect milk to be implicated in the larger epidemics, the special investigation of which constitute the principal source of data on milk. In spite, however, of the fact that the most promising source of information is lacking, sufficient evidence has accumulated to include an inquiry on milk in the recent investigation forms.

1. Wickman (W 21) first suggested milk in connection with an outbreak of poliomyelitis. In the parish of Ukna (population 2200) a case appeared on October 6, 1905. The father of the patient had a dairy farm. Another son, and 4 other children of the neighborhood were stricken with the disease on October 20. Altogether 6 families were attacked and 10 cases occurred. All were supplied with milk by the father of the initial case. Under these circumstances it seemed to Wickman probable that the milk conveyed the infection.

2. Jubb (J 14; J 15) is occasionally cited as having attributed several cases in West Kirby, near Liverpool, to milk. He reported 4 paralytic cases, 3 of whom had the same milk supply, occurring in the fall of 1914, in a population of 14,000. The first patient was the child of a physician who had attended 2 of the 7 cases occurring in 1913. This child did not use the milk supply common to the 3 later cases. The dates of the onset in these 4 cases were: August 10th, September 22nd, October 1st, and October 2nd. Jubb himself, on page 402, says, in answer to a query concerning milk, that he himself was more impressed by the possibility of human carriers, even that one of the distributors of milk may have been the source of infection. The time

intervals between the cases are not suggestive of a common source of infection.

3. The Spring Valley, New York, outbreak. J. C. Dingman (D 13) reported a series of 8 cases of poliomyelitis occurring during July, 1916, in Spring Valley, New York, under circumstances which pointed toward a two-cow dairy as the source of infection. The house and barn of the dairy were in a most unsanitary condition. One case of poliomyelitis developed on the farm on July 4th, another on July 22nd.

The former is believed to have been the source of the outbreak. Six other cases developed in Spring Valley, all with onsets between July 18th and 22nd. These were boarders in three Jewish boarding houses, all from New York City and Brooklyn. Children in these boarding houses who drank milk from other sources, and other children who drank the milk boiled escaped infection. Chart XVIII, constructed by Aycock and Luther (A 49) from Dingman's report makes the relations of this outbreak clearer.

In favor of the infection having been spread by milk, Dingman argues:

(a) All 7 cases had their onset July 20 or 22nd. (Note: In the text, he gives the onsets as: 1, July 18; 2, July 20; 4, July 22.)

(b) All 7 used the milk raw, while those who boiled it escaped.

(c) Children living in the same house but with a different milk supply escaped.

(d) The milk was not chilled but was delivered warm.

(e) At the time these were the only cases within 4 or 5 miles of Spring Valley.

The Mayor's Committee of the New York City Health Department (N 19), however, points out in connection with this outbreak, that the boarders all came from New York and Brooklyn where the 1916 epidemic was at its height and between which cities and Spring Valley there was a constant movement of persons; that the first case was evidently a contact case. They argued from this that contact infection was probable in the other cases as well.

4. The Cortland, New York, outbreak. Knapp, Godfrey and Aycock (K 17) report an outbreak at Cortland, New York, the explosiveness of which suggests a common source of infection. The evidence points to milk as this source. In Cortland between December 14th and 25th, 1925, there developed 8 cases of poliomyelitis. The



first patient in the December series became ill on December 7th. He was a 16 year old boy employed as a milker on a dairy farm, and, although ill, he continued to milk 8 to 10 cows as usual from December

CHART XVIII  
 EPIDEMIC OF POLIOMYELITIS  
 PROBABLY MILK-BORNE  
 SPRING VALLEY, NEW YORK, 1916

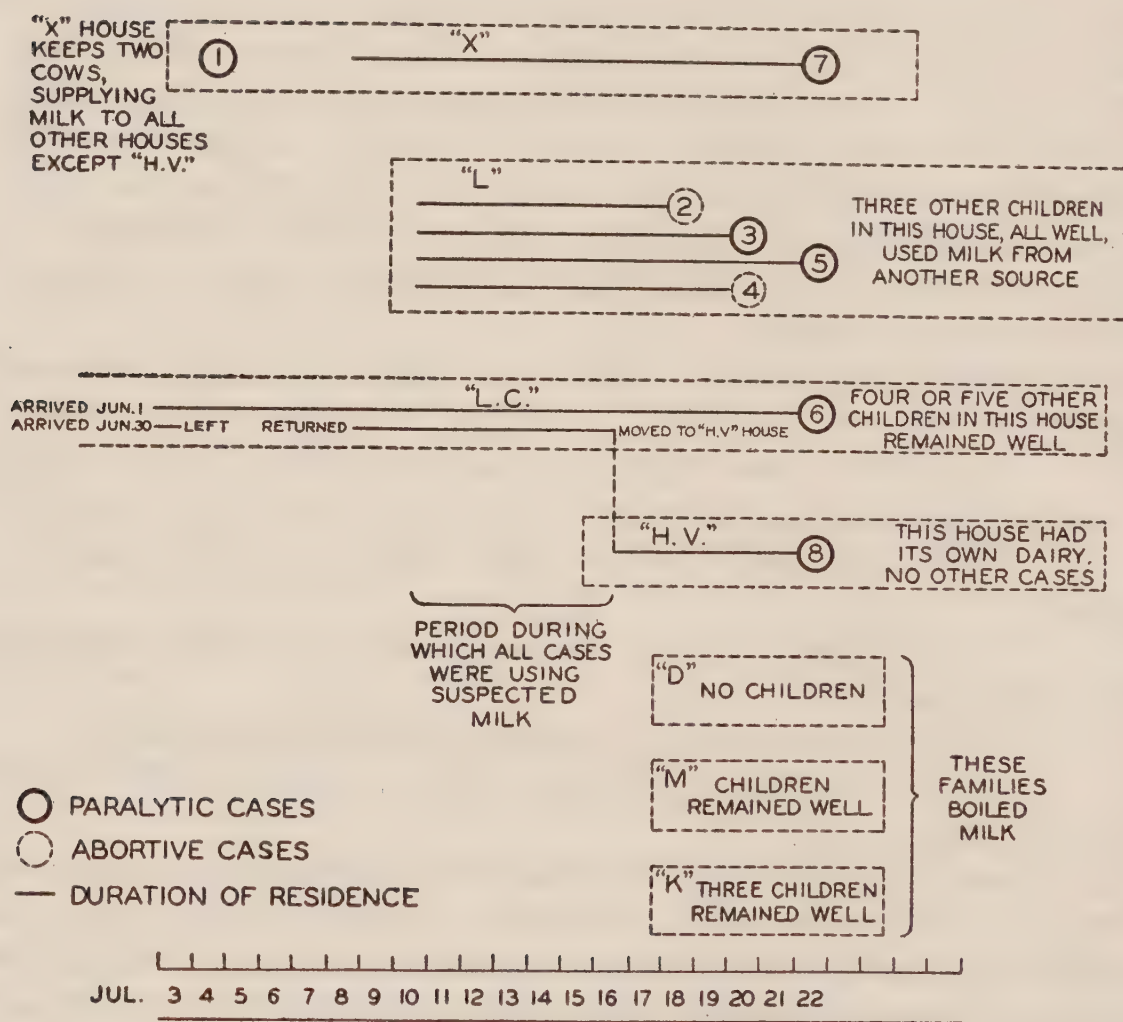


CHART XVIII. The circles represent cases. The horizontal lines preceding the circles represent length of residence and, except in H. V. house where milk was not used, the period during which the milk supply was used. After chart made by Aycock and Luther (*J. Prev. Med.* 3: 109, 1929) from data of Dingman (*New York State J. Med.* 16: 589, 1916).

7th to December 10th. Table 81 summarizes the age, sex, outcome and date of onset of these cases.

All these cases were paralytic, and no nonparalytic cases were dis-

covered. In no instance could direct contact with a previous case be shown, and in only two instances could indirect contact be traced. Cases 2 to 8 were definitely proved, and case 9 shown probably to have consumed milk from a dealer who distributed milk from the farm where Case 1 worked.

The authors summarize the outbreak:

"As to the Cortland outbreak, we would point out that the only cases to occur in a city of 15,000 people subsequent to the appearance of three cases more than two months previously, were, with one possible exception, in persons who drank milk from one dealer who sold less than 4 per cent of the city's total supply; that the cases were distributed widely enough to make it improbable for the milk supply to be a mere

TABLE 81  
POLIOMYELITIS CASES, CORTLAND, NEW YORK, DECEMBER, 1925\*

| CASE | AGE       | SEX | FATAL | DATE OF ONSET |
|------|-----------|-----|-------|---------------|
| 1†   | 16 years  | M.  | —     | December 7    |
| 2    | 15 months | M.  | —     | December 14   |
| 3    | 22 years  | M.  | +     | December 16   |
| 4    | 2 years   | F.  | —     | December 16   |
| 5    | 3 years   | F.  | —     | December 18   |
| 6    | 11 years  | M.  | +     | December 18   |
| 7    | 17 years  | M.  | —     | December 19   |
| 8    | 7 years   | M.  | —     | December 25   |
| 9    | 19 years  | M.  | —     | December 25   |

\* Knapp, Godfrey and Aycock, J. A. M. A. 87: 635-639, 1926.

† Presumably the source of infection.

coincidence of geographic distribution. When to these facts we add that an acutal paralytic case of the disease existed on the dairy farm from which most of the milk came; that this patient was milking the cows and handling the milk for a period of four days while in the acute stage of the disease, and as the time which elapsed between this period and the dates of the onsets of the subsequent cases was consistent with the generally accepted minimum and maximum incubation periods of poliomyelitis, the chain of circumstances is as complete as is found in the majority of milk-borne outbreaks of other diseases."

5. The Broadstairs, England, epidemic. Aycock (A 33) reports an epidemic which occurred at Broadstairs, England, in October, 1926, where the evidence pointed toward transmission by milk.



Broadstairs is a city of some 15,000 population. In the 5 years previous to 1926, only 2 cases had occurred there (in 1925). The epidemic was explosive in nature, 62 cases being reported between October 10th and 29th, 42 of them during the week of October 10th.

Chart XIX shows the explosiveness of the outbreak, especially if the paralytic cases only are considered.

Outstanding features, in addition to the suddenness and severity of the outbreak, were the occurrence of multiple cases in private boarding

CHART XIX  
POLIOMYELITIS  
CASES BY DATE OF ONSET  
BROADSTAIRS, ENGLAND, 1926

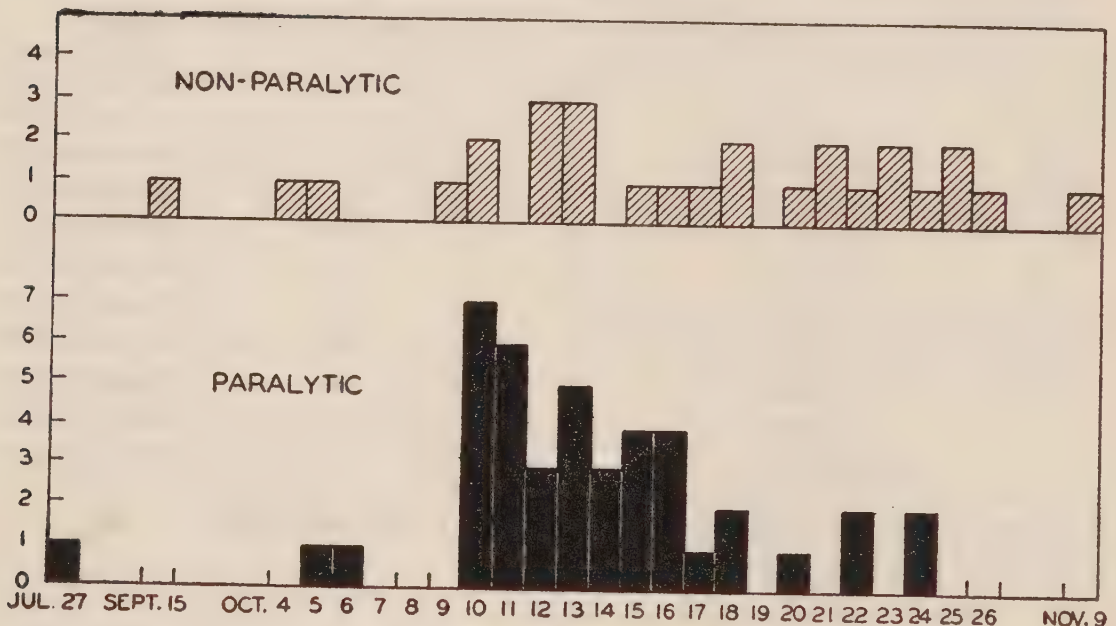


CHART XIX. Epidemic of poliomyelitis, Broadstairs, England, 1926. The explosiveness of the outbreak, especially if the paralytic cases only are considered, points toward transmission by milk. (From Aycock, *Am. J. Hyg.* 7: 791, 1927.)

schools having little communication with the town or with each other, and the fact that only the well-to-do class of the population was affected; moreover, the epidemic was confined strictly to Broadstairs and did not extend to adjacent cities.

The milk supply: Investigation disclosed that all of the paralytic cases both among the residents of Broadstairs and in the schools, used milk from one dealer, either directly or indirectly through a distributor who purchased milk from him daily from September 23rd to October

15th. All the abortive cases except 3 also used this milk, as well as 1 case in which the paralysis was unknown. Moreover, 3 visitors, who left Broadstairs just previous to the outbreak, and who developed the disease in widely separated places during the height of the epidemic, had also drunk this milk.

Unfortunately, time did not permit the author to investigate the 15 farms from which this dealer purchased his milk, and no report is made as to a possible source of contamination.

A. S. MacNalty (M 9a) did not agree that milk was responsible for this outbreak. His arguments are, (a) that contact was traced in a large number of instances, (b) that no source of contagion was found on the farms or among the distributors of the milk, and (c) that many of the inhabitants of Broadstairs drank the milk and remained well.

The explosive character of the epidemic he finds hard to explain. He surmises that the other outbreaks in England had caused an influx of carriers into Broadstairs, and that the carrier rate rose until it reached a point at which the virus became actively virulent in a susceptible juvenile population, and quotes Glover's work on cerebrospinal fever for an analogy.

6. H. Davide (D 6) has been quoted as attributing a small outbreak in North Sweden to milk. The facts, however, were, that a dairy maid developed poliomyelitis, and continued to milk cows during the acute stage of her illness. Davide points out that if milk were a particularly adapted agent for the transmission of contagion, one would have expected to see an explosive outbreak among the other residents of the farm, who had all drunk the milk. Actually, however, this did not occur. Some children, however, who stayed much with the servant, playing about the stable and helping her to milk the cows, were attacked, and considerably later other cases developed on the farm.

7. Melbourne, Australia. Dr. Jean Macnamara has sent to us the particulars of a group of 3 cases, occurring in an outlying suburb of Melbourne, in which it seems probable that the infection was conveyed to the 2 latter cases through milk, infected by the father of the first case. On November 22, 1930, R. W., aged 5 years, developed an illness, which extended to paralysis 2 days later and to death on November 30th. Until removal to the hospital, November 24, the boy was cared for by his father, M. W. The father's work involved the bottling of milk, bought in bulk, and distributing it in a horse-drawn cart to the homes of customers in the district. The amount distributed, or the number of customers is not available. At the end of November or



early in December (the mother was uncertain as to the date) C. M., a 3½ year old boy, who had regularly drunk milk from M. W.'s supply, was taken ill, and was later paralyzed. On December 5, 1930, a second paralytic case developed in a boy, aged 2 years, 11 months, who had also drunk the milk from M. W.'s supply for a month previously, usually unboiled.

8. Rosenow (R 49) reported 8 frank and several abortive cases of poliomyelitis in a midwestern college which he attributed to milk.

**Age Incidence in These Epidemics.** The age incidence in the Cortland and Broadstairs outbreaks is interesting. In the former, the ages, excluding the 16 year old dairy hand who presumably was the source of infection were 15 months, 2, 3, 7, 11, 17, 19 and 22 years.

TABLE 82  
AGE DISTRIBUTION OF CASES IN BROADSTAIRS, ENGLAND, OUTBREAK OF  
POLIOMYELITIS, OCTOBER, 1926\*

| AGE GROUP           | ALL CASES | CASES IN<br>RESIDENTS | CASES<br>IN BOARDING<br>SCHOOLS |
|---------------------|-----------|-----------------------|---------------------------------|
| Under 5 years.....  | 10        | 9                     | 1                               |
| 5 to 9 years.....   | 17        | 12                    | 6                               |
| 10 to 14 years..... | 32        | 11                    | 21                              |
| 15 to 19 years..... | 4         | 4                     | 1                               |
| 20 to 24 years..... | 4         | 2                     | 2                               |
| 25 to 29 years..... | 4         | 2                     | 2                               |
| 30 to 34 years..... | 1         | 0                     | 1                               |

\* Aycock, Am. J. Hyg. 7: 791, 1927.

While the Broadstairs outbreak showed an increased age incidence, the age at risk was not typical, since the outbreak affected largely boarding schools. Aycock, therefore, in Table 82 has divided the cases into those in the schools, and those in the residents of Broadstairs. Among the residents, however, this same increased age is noted.

In the 2 cases which were noted by Macnamara in Melbourne, the ages were 3½ years, and 2 years, 11 months.

Godfrey (G 11) has directed attention to the characteristic increased age incidence in milk-borne epidemics of scarlet fever and diphtheria. It is interesting to note that, although obviously no conclusions can be drawn from such scant data, the ages of the Cortland and Broadstairs outbreaks are at least in line.

**Conclusions.** (Stallybrass (S 53, p. 382) quotes an anonymous writer

in the *Lancet* (E 9a) who lays down the following criteria by which a milk-borne epidemic may be recognized:

1. Epidemiological or bacteriological evidence that the disease in question is transmissible by milk.

2. Suddenness of onset.

3. A milk supply common to a preponderating majority of the earlier cases.

4. The presence of a sufficiently large community of persons who are not consumers of the milk to serve as controls.

5. The absence of any obvious link, other than the milk supply, between the earlier cases.

6. An unusual age distribution of the cases.

7. The demonstration of a source from which the milk supply might have become contaminated.

In the case of poliomyelitis, (1) has been discussed above, and the transmissibility of the virus by milk conceded as possible.

As to (5), in a disease where it is the exception rather than the rule for obvious links to occur between cases, this criterion is meaningless.

It may, however, be relevant to call attention to the fact that three of these epidemics occurred in years and localities where epidemic conditions prevailed, and the virus was presumably widespread. The Swedish cases occurred in 1905, a year in which the number of cases in Sweden has been exceeded only in the great epidemic of 1911–1913. The Spring Valley, New York, outbreak occurred in 1916 at the height of the largest epidemic so far recorded. The Broadstairs outbreak occurred in 1926, the peak year for England.

To this observation the Cortland outbreak is an exception. Although 1925 did show in New York State an increase from a normal expectancy of 542 cases to 793 cases, on the other hand the Cortland outbreak occurred in December, when only 26 cases were recorded for the whole State of New York.

Omitting therefore (1) and (5), and applying the other criteria to the above four outbreaks where the evidence pointing toward milk is the strongest, we find:

1. The Swedish outbreak, 1905 (Wickman), fulfills (2), (3), and (7), while (4) and (6) are not reported on.

2. The Spring Valley outbreak, 1916 (Dingman), fulfills (2), (3), (4), and (7); (6) is not reported upon.

3. The Cortland, New York, outbreak, 1925 (Knapp, Godfrey and Aycock), fulfills all of the *Lancet* criteria.



4. The Broadstairs outbreak, 1926 (Aycok), fulfills (2), (3), (4) and (6); (7) is not reported upon.

Stallybrass (S 53, p. 403), in reviewing these reports, says: "Although the conveyance of this disease through contaminated milk can not be regarded as generally accepted, the author regards the evidence as very strong."

The Section on Communicable Diseases of the White House Conference (W 18) says: "There is substantial evidence of spread by milk, but this mode of spread is an unusual one."

### Water

In many of the earlier reports, the possibility that the virus of poliomyelitis might be water-borne was considered. Later, when the experimental evidence seemed to preclude such a possibility, the matter was dropped. Recently, however, Kling, by advocacy of his "hydric theory," has caused the subject to be reopened, and considerable attention has been given to it in Europe.

Kling (K 11) bases his hydric theory upon a belief that the point of entry of the virus is intestinal, and that the feces are infective. These points were considered earlier in this chapter, as was also the effect of chlorination of water upon the virus.

**Epidemiological Arguments.** The epidemiological arguments most often advanced in favor of the theory that poliomyelitis is water-borne are:

(1) That the curve of seasonal distribution is similar to that of typhoid.

(2) That the disease follows the waterways rather than the railways.

Kling advances in support of his theory a number of observations made in Sweden in 1905 and 1911-1913, and in Saxony and Roumania in 1927. He cites in support of his theory:

(1) When poliomyelitis makes its appearance in a focus, it always appears in the neighborhood of a water system.

(2) The formation of foci is determined by the water system. Railway systems do not play a rôle of primary importance. Likewise foci are never found in the plains between water-courses, where railroads are numerous.

(3) In countries where both cities and rural districts are present (such as Sweden and Roumania) the latter are more commonly affected. A city may even be included in a focus without being attacked.

(4) When poliomyelitis spreads over a large area, it begins in the

plateau which gives rise to water courses, and reaches the plain by following the direction of the water bed.

(5) The foci belonging to the same water system are in a general line but are not continuous. Often they are separated by a considerable distance.

(6) The relation of the foci is determined by the course of a stream, or by the contour of a lake. However, they sometimes extend rather far from the chief stream. It remains to be decided whether this fact depends upon geological, geographical, or biological conditions.

Kling also states that the Swedish villages which filter the surface water for drinking were more often attacked (36.8 per cent) than those that use ground water (6.6 per cent). In the cities located in infected areas, this was even more marked, as is shown below:

#### ALL SWEDISH VILLAGES, 1911\*

| <i>Total Number of<br/>Cities</i> | <i>Origin of Water</i> | <i>Number of Cities<br/>Having Epidemics in<br/>1911-1913</i> | <i>Per Cent</i> |
|-----------------------------------|------------------------|---------------------------------------------------------------|-----------------|
| 60                                | Ground                 | 4                                                             | 6.6             |
| 38                                | Surface                | 14                                                            | 36.8            |

#### CITIES IN SWEDEN LOCATED IN POLIOMYELITIS FOCI OR THEIR IMMEDIATE VICINITY, 1911-1913

| <i>Number of Cities</i> | <i>Origin of Water</i> | <i>Number of Cities<br/>Attacked by Epidemic<br/>Poliomyelitis</i> | <i>Per Cent</i> |
|-------------------------|------------------------|--------------------------------------------------------------------|-----------------|
| 21                      | Ground                 | 4†                                                                 | 19              |
| 22                      | Surface                | 14                                                                 | 63.6            |

\* Kling, Svenska läk.sällsk. handl. 55: 23, 1929.

† Two of these had very low rates.

These epidemiological observations seem to Kling to point toward water as a factor in the spread of poliomyelitis.

Levaditi, Schmutz and Willemin (L 51) in their study of the 1930 epidemic in Alsace report that the earliest cases appeared sporadically in widely separated points, and no direct or indirect relationship could be established. Except in the large urban centers, no relationship existed between the population of the affected regions and the total morbidity; towns very near contaminated ones remained exempt despite the probability of frequent relations among their inhabitants; no reasons could be found for a certain clear *regional* immunity. The epidemic conferred a refractory state as it spread; the foci showed marked predilection for water-courses; so far as could be judged there was a manifest tendency to *ascend* streams (affluents of the Rhine). The foci preferred the lowlands, moist regions with areas of surface water; they were arrested at the first foothills of the mountains.



The epidemic flourished especially in regions fed by surface water, apparently irrespective of its purity or contamination.

They conclude that as a whole the observations of the commission support the theory of propagation of poliomyelitis through contact, but it does not in itself suffice. Some other factor must intervene, and it must be sought in particular local conditions, either meteorological or geological.

Numerous examples may be cited of the peculiar local selectivity of poliomyelitis. Lavinder, Freeman and Frost (L 16) say, as to the irregular geographic distribution of epidemic foci, "Most of the epidemic diseases of man, even when transmitted by the lower animals or by insects, are disseminated along routes of travel; and in their spread from a given point are naturally expected to follow along the more important of such routes. It has often been noted, however, that epidemics of poliomyelitis not infrequently display great irregularity in this connection, and do not always show the distribution to be expected as the result of dissemination along the main highways of traffic.

"For example, in 1910, there occurred a rather severe epidemic in Washington, D. C., and a proportionately smaller outbreak in Philadelphia, while Baltimore, lying between these two cities, and in daily communication with each, escaped with nothing more than a moderate increase in the number of sporadic or endemic cases. In the epidemic of 1916, New York City and Newark, N. J., both suffered from severe epidemics, yet Jersey City, lying between the two and in intimate daily contact with both, suffered no worse relatively than Baltimore in 1910. Numerous similar instances might be cited from many different epidemics. These instances alone suggest that epidemics may be due to a '(place infection),' not transferred by human travel—an infection of local water or food supplies, of insects or domestic animals, whose range of travel is more limited than that of man."

Aycock (A 34) has expressed a somewhat similar view when he says that "only a small fraction of persons exposed to the virus, due to some as yet undetermined departure from the normal, are susceptible to the disease. That variations in susceptibility may be due in part to some very general factor, is indicated by the simultaneous rise and fall in the occurrence of the disease in communities so far separated that communication of the same strain of virus hardly suffices for an explanation; on the other hand, that this factor may likewise operate over restricted areas is shown by the occurrence of intense outbreaks in certain localities surrounded by areas practically free from the disease."

### Water as a Factor in Host Resistance

Under periodicity, we have mentioned the fact that some cities seem to remain peculiarly free from epidemic poliomyelitis, though sporadic cases are constantly present. Certain cities, on the other hand, seem to suffer from almost biennial outbreaks.

The possibility that water might be implicated in the epidemiology of poliomyelitis without actually conveying the virus has not, so far as we are aware, been suggested in the literature. It does not seem impossible that water might be a greater or less factor in determining susceptibility or resistance to poliomyelitis. If (see under *The Host*) susceptibility should be proved to lie in some endocrine abnormality, water might very conceivably bear a causal relationship to such an imbalance. One instance of an endocrine disturbance caused by water is generally conceded—that is, endemic goiter. The possibility exists that a water supply might determine the degree of susceptibility of a locality, and account for the anomalies of what Levaditi termed “regional immunity” and which has been an inexplicable phenomenon on the basis of differences in exposure.

### FOMITES

Indirect contagion, or transfer of infection by inanimate objects or fomites, is theoretically possible in any disease in which infection may be effected by direct contagion. The probability of indirect transference will vary with the resistance of the etiologic agent to conditions outside the human body, especially with its resistance to drying.

Under *Properties of the Virus*, in the *Chapter on Etiology*, the question of resistance of the virus of poliomyelitis has been fully considered. It is sufficient to say here that under experimental conditions, the virus has proved very resistant to drying, when the temperature has been kept low. Rhoads (R 7) has reported an extreme instance where the virus survived for 8 years in 50 per cent glycerol at 4°C., the virulence remaining essentially unchanged. Leiner and von Wiesner (L 28, II and IV) on the other hand, found that drying thin films of emulsion for 4 hours at a temperature at 37°C. will destroy the virus.

The trend of medical thought has of late, however, been away from such indirect dissemination of infection in the contagious diseases and toward direct person to person transfer through infective droplets. Stallybrass (S 53) points out that the evidence bearing upon the transmission of such diseases as scarlet fever and diphtheria by fomites mainly antedates the discovery of human carriers and must be re-



garded as suspect. He believes that "the epidemiological evidence is that fomites, in the restricted sense of objects retaining infection for anything more than brief periods, play but little part in the transmission of infection, even when, theoretically, the possibility must be admitted."

Josefson (J 13), Wickman (W 21), and Parhon (P 1a) described instances in which the infection was believed to be so spread.

The fact that Barren Island, New York (N 20) had not a single case of poliomyelitis in 1916 is cited as an argument against transmission of the virus by inanimate objects. Barren Island lies in Jamaica Bay between Rockaway Point and the Flatlands, and was, in 1916, the dumping ground for the refuse from New York City. Some 800 persons who rarely visited the mainland lived on it, about 350 of them children under 16 years of age. Flies and mosquitoes were abundant, rats numerous. Although all the refuse, rags, and dead animals from New York City were sent there, no case of poliomyelitis developed on the island.

Second cases of the disease have from time to time been observed to occur in a house at varying intervals after the first case. It is impossible to consider these isolated instances quantitatively, to judge whether they are more numerous than would be expected from chance distribution. They suggest the possibility of a chronic carrier rather than persistence of the virus.

#### INSECT TRANSMISSION

Certain epidemiological features of poliomyelitis early suggested insect transmission. For this reason, numerous attempts were made to demonstrate such a possibility, but the results have been negative, and the theory has been abandoned by most epidemiologists. The present consensus of opinion is that insects play no part as active biological agents in the spread of poliomyelitis and a very subordinate one at most in the mechanical transfer of the virus.

**Biological Transmission.** *Experimental Evidence.* To lend support to this theory, the minimal confirmation to be sought experimentally would be: (1) proof of the presence of the virus in the blood of human beings, (2) the ready production of the disease experimentally by the intravenous, or less possibly by the subcutaneous or intradermal, route, (3) finding of the virus in suspected insects, (4) the actual production of the experimental disease by the feeding of insects upon infected and subsequently upon normal animals.

(1) The virus of poliomyelitis has never been detected in the blood

of human beings, and only rarely in the blood of monkeys with the experimental disease. These results are considered fully under *Distribution of the Virus*, in the *Chapter on Etiology*.

Kling, Pettersson, and Wernstedt (S 67) moreover, argue that the virus can not exist in the blood after the acute stage, since after the first week neutralization bodies are frequently present in the blood. Therefore, transplantation of the virus from the blood would always presume the existence of acute cases.

(2) Production of the experimental disease by the intravenous route:

(a) It is only when overwhelming quantities (50 cc. or more) of an active virus are injected into the blood of monkeys that infection occurs, and even then if the central nervous system is intact, infection is inconstant. (See under *Routes of Inoculation*).

(b) The possibility must be considered that in boring for blood, the proboscis of an insect must pierce the dermal and subcutaneous tissues. Although the amount of virus which could be thus deposited in these tissues would be extremely small, positive inoculations have been obtained by both routes. Flexner and Lewis (F 41) were the first to report success by subcutaneous injection, but others have obtained infection by this route only with difficulty. (See under *Routes of Inoculation*).

Brodie of McGill University (personal communication) reports that he obtains consistently positive results by intradermal injection of a potent virus.

(3) With one single exception, attempts to demonstrate the virus in extracts of insects which had fed upon either human beings or monkeys with poliomyelitis have been negative. Howard and Clark (H 31) experimented upon lice, both *Pediculus vestimenti* and *Pediculus capitis*. The results were negative. These authors also attempted to infect monkeys with filtrates of bedbugs, *Cimex lectularis*, which had fed upon infected monkeys. In one instance out of 16, they obtained positive results. The filtrate of a bedbug which had fed upon an infected monkey 7 days previously, produced the experimental disease. The authors were unable to repeat this experiment, but the interesting fact remains, that in one instance, a biting insect took up virus from the blood and maintained it in a living state for 7 days.

Kling, Pettersson, and Wernstedt (S 67) performed similar experiments with extracts of fleas, collected from human patients. The results were negative.

Noguchi and Kudo (N 32) also carried out experiments with non-



biting flies, the domestic house-fly, *Musca domestica*, and the blue-bottle fly, *Calliphora vomitoria*. A number of young larvae were fed with the brain tissue of a *Macacus rhesus* which had died of typical experimental poliomyelitis, and were allowed to hatch. No trace of the virus of poliomyelitis was demonstrable in the filtrate of an emulsion of the adult flies and pupae. They concluded that not only was it improbable that the virus was taken up by the larvae and multiplied in them, but also that it is in all probability rapidly destroyed within the body of the insect.

(4) Attempts to transfer the disease to monkeys through the bites of insects have likewise yielded negative results:

(a) Mosquitoes: Noguchi and Kudo (N 32) attempted to transmit the disease to monkeys by *Culex pipiens*. They first fed young growing larvae with poliomyelitis virus in the polluted water in which they were grown, the adult mosquitoes being allowed to feed on a normal *Macacus* monkey. The results were negative. (Note: Professor Brues of Harvard University has called our attention to the fact that infection of larvae characteristically does not survive the profound biological transformation involved in metamorphosis.) Noguchi and Kudo used the more ordinary method of allowing the mosquitoes to feed upon an infected and subsequently upon a normal animal. This method also yielded negative results.

(b) Flies: Rosenau and Brues (1912, R 34) announced that by allowing thousands of the biting stable fly, *Stomoxys calcitrans*, to feed first upon an infected and immediately afterward upon a normal *Macacus* monkey, they had transmitted the disease to the latter. Anderson and Frost (1912, A 27) reported that they had confirmed these findings, but later (A 28) announced that they were unable to obtain further positive results. Howard and Clark (1912, H 31) were likewise unable to transmit the disease in this way. Brues himself (N 20) later, in 1916, said, "These experiments have failed of further confirmation, and cannot now be regarded as free from possible error."

(c) Lice and bedbugs: Howard and Clark (H 31) in the course of the above experiments on filtrates from lice and bedbugs sometimes allowed the insects to feed upon normal monkeys, when no infected monkeys happened to be available at times when a feeding was necessary to keep them alive. During the varying intervals occurring after the last feeding on infected animals, normal monkeys were also used to keep the insects alive. While this was not a definite attempt to study direct transmission by means of these insects, it is worthy of note that none of the normal animals so used ever showed symptoms of the disease.

*Conclusions.* A quantitative consideration of these experimental results—the failure to demonstrate virus in the blood of human beings at any stage of the disease; the very inconstant presence of even a small amount of virus in the blood of monkeys, however inoculated; the necessarily short survival of virus in the blood of cases, either of human beings or monkeys; the failure, with one exception, to demonstrate virus in the filtrates of insects; the large amount of virus required to produce even inconstant infection by the intravenous route—and a consideration of the amount of blood which a blood-sucking parasite could be expected to transfer, seem to exclude the theory of insect transmission. The whole of the experimental evidence is negative.

*Epidemiological Evidence.* Certain epidemiological features of poliomyelitis have been suggestive of spread by insects. These may be briefly outlined:

(1) It has been characteristic of outbreaks of poliomyelitis that only a small percentage of cases can be traced to previous cases (see *Direct Contact*) and that the increase in incidence among those known to have been exposed, whether in families, institutions, or hospitals, has been low (see *Multiple Cases*). These features are common to insect-borne diseases, but have been difficult to reconcile on the basis of contagion (see *Latent Immunization*).

(2) Certain facts in the spatial distribution of poliomyelitis have also suggested an insect vector: The rural distribution equals, if not exceeds, the urban incidence.

The sporadic cases occurring apparently without reference to previous cases, and not giving rise to subsequent cases have been explained by some on the basis of an animal reservoir and insect intermediary.

Brues (N 20) in his study of the 1916 epidemic of poliomyelitis in New York City noted: that cases were more numerous around the waterfront; that the disease was more apt to spread through a block than across a street, although streets constitute the playgrounds of the children, and mingling of children is with those of opposite sides of the street; that the spread of the disease from Brooklyn was radial, and was halted by the East River, not following the daily migrations of the human population into Manhattan. Brues believed that these facts were more logically explained on the basis of rats as an animal reservoir and fleas as the intermediary than on the basis of person to person transmission.

On the other hand, in the same epidemic, Emerson (N 20) emphasized that the disease did not select those of low economic status. This alone



would rule out lice and bedbugs. While anyone may accidentally harbor either, statistically speaking, they accompany filth and poverty.

(3) The seasonal incidence of poliomyelitis coincides in general to that of greatest insect prevalence and the incidence of the insect-borne diseases. Conversely it does not coincide with the seasonal incidence typical of the droplet contagions.

For an insect to be the sole means of the transmission of poliomyelitis, however, it must not only abound at the season of greatest prevalence of the disease, summer and early fall, but it must not wholly disappear at any season, since sporadic cases occur in every month of the year. Epidemics have, moreover, extended into midwinter. Leake, Bolten, and Smith (L 20) have collected reports of 39 such outbreaks, which are summarized under seasonal incidence. The variety of insects which could be the sole vector is therefore greatly limited, and excludes from practical consideration outdoor insects. The cold of autumn puts an abrupt limit to the further progress of diseases spread by outdoor insects, as malaria and yellow fever. Those insects which are parasitic upon man or a lower animal are, however, not so sensitive to temperature, and Brues has cited this fact as a further argument in favor of his theory of spread by rats and fleas.

**Mechanical Transmission.** The above arguments apply to insects as the active agents of transfer. Passive transfer by mechanical carriage of the virus has also been suggested. Such transfer might be merely accessory to contact infection.

Flexner and Clark (1911, F 32) allowed flies to feed upon the cords of recently paralyzed monkeys, and showed that they harbored the virus, either as a superficial contamination or in the gastro-intestinal tract, in an infectious state for at least 48 hours. Howard and Clark (1912, H 31) showed that the domestic fly can carry the virus of poliomyelitis in an active state for several days upon the surface of the body, and for several hours in the gastro-intestinal tract.

Frost (F 71) argued from the similar seasonal distribution and similar age incidence that the same or allied causes may contribute to poliomyelitis and infantile diarrhea. The similarity of the curve of poliomyelitis outbreaks to that of summer typhoid has also been pointed out and advanced as an argument in favor of mechanical transmission of the virus by flies.

Brues (N 20), on the other hand, in New York City in 1916, observed carefully the areas and streets which were especially infested with flies, and found that their prevalence was not reflected in the incidence of poliomyelitis.

# TOPICAL ANALYSIS

## CHAPTER I

### HISTORICAL SUMMARY

Ancient Records.

Development of Modern Conception of Poliomyelitis.

Period of Clinical Observation: The pre-Heine period before 1840; first edition of Heine's monograph, 1840; the Heine period (1840-1860)—additional clinical contributions, beginning of pathological speculation; second edition of Heine's monograph, 1860—spinal lesion proposed on ground of functional disturbances.

Period of Pathological Investigation, Cornil to Wickman: first microscopical examination; Charcot's interpretation; diverse views regarding site of primary lesion; first use of the term poliomyelitis; cases in the acute state; portal of entry; conceptions of pathogenesis.

Period of Epidemiological Interpretation, 1890-1907: the first groups of cases; infectiousness established by Medin; transmission by person to person contact accepted following Wickman's report.

Period of Experimental Contribution, 1908 to the present.

## CHAPTER II

### ETIOLOGY

Introductory note.

Bacteriology.

Early bacteriological investigations—Negative results; Positive results.

Bacteriological studies during the "Experimental Period"—Negative results; The Streptococcus—Etiological significance, Argument for the streptococcus; Argument against the streptococcus, Cultural and morphological tests, Resistance to glycerin, Effect of concentration, Effect on spinal fluid sugar, Immunity tests, Attempts at the transmission of poliomyelitis to animals with cultures of streptococci; Cultivation of the virus—"Globoid Bodies."

The Virus.

Preliminary experiments—Early experimental work; Transmission of poliomyelitis to monkeys, Landsteiner's original experiment, Transmission in series.

Properties of the virus—Filterability, size; Preservation in glycerin; Resistance to drying; Resistance to freezing; Effect of heat, Body temperature, Temperatures above 37°C.; Effect of light; Effect of chemicals—Disinfectants—Bichlorid of mercury, Formaldehyde, Oxidizing agents, chlorin, hydrogen peroxid, potassium permanganate, Phenol, Antiseptics—Menthyl, thymol, hexylresorcinol; Ether, Miscellaneous, Chemotherapy; Conservation of the virus in water, milk or butter—Conserva-



tion in water, Conservation in milk, Conservation in butter; Action of bile; Action of gastric and intestinal secretions; Action of nervous tissue; Effect of dilution and of certain tissue constituents; Optimum hydrogen ion concentration; Electrical charge of the virus; Adsorption, elution and purification of the virus; Concentration of the virus; Titration of the virus; Survival of the virus in a refractory host; Effect of vaccine virus; Production of toxin; Strains—Variations in virulence.

Distribution of the virus in the body—Central nervous system; Spinal, Gasserian and abdominal sympathetic ganglia; Peripheral nerves; Cerebrospinal fluid, Human, Monkey; Blood, Human, Monkey; Lymph nodes, Mesenteric, Other lymph nodes; Tonsils and mucous membrane of the nasopharynx; nasopharyngeal secretions or washings, Monkeys, Human cases—Patient with disease or after death, Healthy contacts; Active carriers—persistence of the virus in the nasopharynx; Tracheal secretions or mucous membranes; Intestinal secretions and mucous membranes; Feces; Other locations.

Persistence of the virus in the body—Nasopharynx, Spinal cord, Monkey testicle.

Routes of inoculation—Intraperitoneal, Intracerebral, Intraneural, Intraocular, Intrasplinal and intracisternal, Intravascular, Peripheral lymph nodes, Cutaneous, Subcutaneous, Intracutaneous, Intrapleural, Intranasal, Intratracheal, Gastro-intestinal.

The Experimental Disease—Susceptibility of monkeys; Clinical history, Incubation period, Symptomatology; Types, Spinal, bulbar, and cerebral types, Abortive type, Relapsing cases; Laboratory findings—Spinal fluid, Cytology and protein content, Colloidal gold test—Clinical examination of the blood, Cytology, Sedimentation velocity; Experimental studies in Therapy—Chemotherapy. The action of subdural injections of epinephrin, Artificial fever, Effect of Roentgen rays, Serum treatment.

The transmission of poliomyelitis to animals other than monkeys—Rabbits, Summary, Conclusion; Other animals, Summary, Conclusions.

### CHAPTER III

#### RESISTANCE AND IMMUNITY

Mechanisms of defense.

Immunity.

Immunity following an attack of the disease—Resistance to re-infection; Neutralization *in vitro*.

Distribution of neutralizing substances in the body—Blood; Spinal fluid; Nasal secretions or washings; Brain; Bile; Stools.

Distributing of neutralizing substances in the animal kingdom—Animals—Monkeys, Normal, Convalescent, Actively immunized; Refractory animals—Normal, Actively immunized; Human beings—Normal, Convalescent. Abortive cases, Frank cases.

The Neutralizing Substances . . . Their properties and nature.

Specificity of the reaction of neutralization.

Allergic reactions.

Complement fixation tests—Spinal fluid, Blood serum.

Precipitin tests.

Stabilization test with gold chlorid.

Colloidal gold test.

Active immunization.

Killed virus.

Attenuated virus—Attenuation by heat; Attenuation by drying; Attenuation by chemicals; Phenol, Formaldehyde, Sodium recinoleate, Aluminum hydroxide; Attenuation by dilution; Attenuated strains.

Living unattenuated virus—Immunization by subcutaneous injection; Immunization by cutaneous or intracutaneous methods, Scarification, Intracutaneous injection; immunization by the intracerebral route; Immunization by the gastro-intestinal route; Immunization by intrasplenic injection; immunization by miscellaneous routes.

Immunization with combinations of virus and immune serum—Serum-virus mixtures with human or monkey serum; Serum-virus mixtures with sheep or horse antipoliomyelitic serum; Administration of virus and immune serum combined.

Immune sera.

Human immune sera—Antibody content of normal and convalescent serum; Relative potency of serum from recent cases and from cases of long standing; Effect of storage on the potency of serum; Selection of a potent serum; Preparation of the serum.

Monkey immune serum—Normal and convalescent monkey serum; Serum of actively immunized monkeys; Hyperimmune monkey serum.

Serum of animals refractory to poliomyelitis—Small laboratory animals; sheep and horses; Specific nature of the antiviral substance in horse serum.

Serum Protection and Treatment (Experimental Basis). Passive immunization.

## CHAPTER IV

### SYMPTOMATOLOGY

Evolution of the Clinical Picture.

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Incubation period.

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Relapses and second attacks.

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## CHAPTER V TREATMENT

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Charcot's theory of a primary motor nerve cell lesion; theory of a primary interstitial inflammation; vascular origin.

Rissler's study of pathology of acute cases.

Wickman's studies.

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Upper respiratory mucous membrane or gastro-intestinal tract as the atrium of infection—pathological and experimental evidence.

Acute Stage and Pathogenesis.

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Effect of serum treatment on the central nervous system.

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Localization in anterior horns.

Persistence of inflammatory lesions.

**Intracellular Pathology.**

Inclusion bodies in ganglion cells, specific nature or physiological findings.

Intranuclear bodies in epithelial cells of the respiratory mucosa.

Recent demonstration of inclusions possibly due to a specific reaction.

**CHAPTER VII****EPIDEMIOLOGY***Part I. Epidemiology of the Disease*

Increase in last forty years: apparent or real; explanations for this increase.

Geographic Distribution: notification; effect of latitude; endemic and epidemic rates; rural and urban incidence.

Seasonal Incidence: a summer disease; seasonal expectancy; secondary increase in early spring; seasonal incidence in endemic and epidemic incidence; percentage monthly distribution; the lag with latitude; cold weather epidemics; explanation of seasonal incidence.

Periodicity: irregularity; immunity of affected localities to subsequent epidemics; tendency of poliomyelitis to revisit areas previously affected; explanations.

Incubation Period; reporting; estimates.

Case Fatality: inverse relationship between case incidence and case fatality; influence of age on case fatality—poliomyelitis, and other diseases; as related to density of population; relation to sex; fatality trends.

**Multiple Cases:**

Difficulty introduced by question of inclusion of abortive cases and by lack of knowledge of incubation period; interval between primary and secondary cases; ratio of secondary to primary cases; estimation by method of Chapin; attack rates among susceptibles; urban and rural outbreaks; secondary cases in hospitals, schools and institutions.

**Contact between Cases.****Direct.**

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*Part II. Epidemiology of the Host***Introduction.**

Age Incidence: virgin soil epidemics; specific morbidity rates adjusted to age groups; age incidence and population density; specific morbidity rates adjusted to both age and population density; age distribution as related to latitude; age trends: age in early epidemics, and recent age trends, morbidity and mortality; variations in age distribution during the course of epidemics; poliomyelitis in the first year of life.

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Race: available sources of information; negroes; incidence among nationalities.



Constitutional Factors influencing Host Resistance: susceptibility or resistance may be local; endocrine abnormality; weight; autarcesis; blood groups; inheritance factor.

Neutralization Tests upon Sera of Normal Individuals.

*Part III. Mode of Transmission*

Infectiousness.

Contagiousness: reservoir of virus; epidemiological evidence.

Latent Immunization: primary exposure, result depends upon individual variations in resistance, dosage, virulence, season; secondary exposures; arguments in favor of latest immunization; arguments against latent immunization.

Maturation: two concepts of maturation; arguments in favor; arguments against.

Non-human Carriage.

Milk: experimental evidence; outbreaks attributed to milk: Sweden, 1905; West Kirby, England, 1914; Spring Valley, New York, 1916; Cortland New York, 1925; Broadstairs, England, 1926; Sweden, 1928; Melbourne, Australia, 1930; a midwestern (U. S.) college, 1930; age incidence, conclusions.

Water.

Fomites.

Insects:

Biological transmission: detection of virus in blood; production of experimental disease by intravenous route; extracts of insects; attempts to transfer the disease through bites of insects.

Mechanical transmission.

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The bibliography has been collected and arranged by Miss Elisabeth F. Hutchin, Miss Mary Elizabeth Thorkelson and Miss Helen G. Field.

## ADDENDUM

### PRELIMINARY REPORT OF THE RESULTS OF THE ADMINISTRATION OF NORMAL ADULT SERUM IN THE PROPHYLAXIS OF POLIOMYELITIS DURING THE 1932 EPIDEMIC

An unusual opportunity of testing the prophylactic value of adult blood was afforded to us by the physicians and the Health Officer of Bradford, Pa. One of the research members of the committee (William B. Brebner) visited Bradford shortly after the outbreak of the epidemic (September 10th, 1932) when eight cases had occurred and at that time urged the inoculation of every child under 15 years of age with 10–20 cc. of parental whole blood. The suggestion was acted upon with the most commendable zeal and between September 10th and October 5th about 1300 were so inoculated. During this period 32 additional cases of poliomyelitis occurred, none of which were among the individuals who received injections of adult blood.

The total population of Bradford is about 18,000 and the number of children between the ages of one and fifteen is probably between 4000 and 4500. We realize that at first there were only a portion of the 1300 children inoculated with blood, since these inoculations covered a period of 25 days and, therefore, at the beginning of the test most of the whole child population were uninoculated. In other words, the number of our controls decreased throughout the test, while the number of inoculated increased.

So far as we now know, probably not more than one half of the total number of treated children had been inoculated at the time of the peak of the epidemic. Nevertheless, the experiment is remarkable in that no treated child developed poliomyelitis. We were prepared to see some children develop modified poliomyelitis if they received blood during the incubation period of the disease. When the data are complete we will attempt to determine how much this prophylactic procedure altered the curve of incidence by a comparison of the curve of incidence of this epidemic with that of others elsewhere.





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